VOLUME 15 NUMBER 2

Medical Library

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
FOR THE STUDY OF

INTERNAL SECRETIONS

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MARCH-APRIL

1931

PUBLISHED BI-MONTHLY BY THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, SUITE 1214 WILSHIRE MEDICAL BLDG., LOS ANGELES, CALIFORNIA
ANNUAL SUBSCRIPTION, $6.00 SINGLE COPIES, $1.25

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ENDOCRINOLOGY

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INTERNAL SECRETIONS

Volume 15, Number 2 MARCH-APRIL, 1931 Serial No. 76

THE ASSOCIATION OF DIABETES INSIPIDUS AND DIABETES MELLITUS*

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The term diabetes has been used since the days of Aretaeus to describe a condition characterized by the passage of an abnormally large quantity of urine. He spoke of it as a melting down of the flesh into water. Willis described diabetes in "Pharmaceutice rationale" in 1674, and is usually credited with making the distinction between the saccharine and nonsaccharine forms of the disease. However, this is not exactly true. Willis recognized the sweet taste of urine in certain cases of diabetes which came under his observation, and this established the basis for distinguishing the two forms of the disease. His description is as follows:

"But, that, as many authors affirm the drink to be little or nothing changed, is very far from the truth, because the urine in all (that I have known who hath happened to have it, and I believe it to be so in all) very much differing both from the drink taken in, and also from any humour that is wont to be begot in our Body, was wonderfully sweet, as it were imbued with Honey or Sugar. The occasion of the foresaid error (as I suppose) was the colour of the Urine, which always appears crude, and watry, as of those labouring with the Pica or with the Dropsie." The sweet taste of urine of diabetic patients had been known to the ancient Hindus but through Willis this observation was now brought to the attention of the western hemisphere.

The first record of the classification of diabetes appears in a thesis written in 1778 by Darwin, an uncle of the famous scientist. Darwin described chyliferous diabetes which "may be distinguished by the taste and appearance of the urine, which is sweet, and the colour of whey," aqueous diabetes (probably diabetes insipidus) and "mucaginous" diabetes. The latter, recognized by coagulation of the urine by heating, was no doubt polyuria of chronic nephritis. Cullen, in 1784, mentioned one case of

*Read before the Association for the Study of Internal Secretions, Portland, Oregon, July 8, 1929.

diabetes in which the urine was "perfectly insipid" and referred to the report of another case by Matthew Lister. It was chiefly through Peter Frank, in 1794, that diabetes insipidus became definitely established as a disease entity.

Within more recent times attention has been directed to the possibility of an intimate relationship between diabetes insipidus and diabetes mellitus. Cases have been observed in which the two diseases coexisted or in which there was apparent transition of one disease into the other. Studies on the experimental production of glycosuria and polyuria have also furnished evidence which has been interpreted as an indication of a similar origin. This problem has received considerable attention in German literature, but comparatively little has been written in English.

The value of many of the early clinical reports is questionable because of uncertainty regarding the criteria for the diagnosis of the two diseases, or perhaps one should say, more properly, disease syndromes. Excretion of large amounts of urine does not necessarily indicate diabetes insipidus nor does glycosuria always signify diabetes mellitus. In many of the published reports it is apparent that this distinction has been overlooked. The excretion of a large amount of urine of low specific gravity in cases of chronic nephritis or polycystic disease of the kidney may indicate diabetes insipidus. The polyuria of hysteria may also be difficult to distinguish. These conditions may complicate the course of diabetes mellitus, and may wrongly lead to the suspicion that the two types of diabetes are associated.

Senator, in 1897, described diabetes insipidus as a not uncommon sequel of diabetes mellitus, the excretion of a large amount of urine continuing after control of glycosuria. As von Noorden pointed out, polyuria in such cases may be due merely to the habit of drinking much water. Recent writers have rarely recorded transition from diabetes mellitus to diabetes insipidus. Cases in which such a change apparently occurred have been mentioned by D'Amato, Teschemacher and Lewin but, as indicated by Lewin, the exact status of all these cases is uncertain. In one of his own cases, a concentration test showed that polyuria was not due to diabetes insipidus. Lewin stated, in 1919, that there was no authentic case on record in which true diabetes mellitus was followed by unquestioned diabetes insipidus. Sweeney recently reported a case of diabetes mellitus, however, in which diabetes insipidus developed.

The appearance of glycosuria in cases of diabetes insipidus is said to be comparatively common although the significance of glycosuria is often uncertain. When glycosuria is accompanied by rapid failure and death in coma the diagnosis of diabetes mellitus can be accepted. When glycosuria is small in amount or transitory and not accompanied by symptoms, the existence of true diabetes mellitus may be doubtful. Determinations of blood sugar and tests of glucose tolerance now generally employed make accurate diagnosis possible, but such observations have not been recorded in most cases.

Senator, in 1897, described a case in which a woman, aged forty-three years, had complained of thirst and polyuria since childhood. The volume of the urine was from 12 to 15 liters in one day, and the specific gravity was 1.001 to 1.003. Three years before examination glycosuria (0.3 per cent) was discovered. Progressive failure and death occurred one year later. Blackett, in 1899, reported a case in which diabetes insipidus existed for eight months and terminated in diabetes mellitus with death from coma. The output of urine measured about 3.5 to 4 liters daily with the specific gravity from 1.002 to 1.006. The urine was free from sugar on frequent tests, but intense glycosuria was discovered the day before death. Kuhn reported a case in which the patient experienced sudden thirst and polyuria after operation on the breast in January, 1901. These symptoms continued until May, 1902, when glycosuria (1.8 per cent) suddenly appeared. The glycosuria persisted; the patient failed rapidly, and died eight days later. Heiberg, in 1911, Freund, in 1922, and Schuntermann, in 1930, described the diabetes mellitus of patients who had had unusual thirst and polyuria since childhood. In Schuntermann's case glycosuria was controlled by diet and polyuria was checked by pituitary extract. In the other two cases death occurred from diabetic coma. The status of two cases reported by Evans and Wallis, in 1921, is uncertain. In both cases there was slight polyuria with transient glycosuria but no other symptoms of diabetes mellitus.

Naunyn, in 1906, referred to the occasional mention in the literature of excretion of sugar in diabetes insipidus, but had seen only one example himself. He considered that there was little evidence to indicate a transformation of diabetes insipidus except in cases of diabetes mellitus attributed to trauma or disease of the brain. He quoted the case of diabetes insipidus with transitory glycosuria described by Hadra and Meliczky in which the disease followed epidemic cerebrospinal meningitis. Teschemacher described a case in which diabetes insipidus followed encephalitis at the age of four years. Intense glycosuria was present for a short time at the onset, and again at the age of seventeen, but was absent at other times in spite of a liberal diet. In this connection the case of French and Ticehurst is of interest. A man who had a fracture of the basisphenoid in 1901 suffered from bilateral temporal hemianopsia, polydipsia and polyuria. The volume of urine averaged 7.5 liters; the specific gravity was 1.004. The urine was free from sugar even after administration of 700 gm. of carbohydrate in one day. In September, 1904, a small amount of sugar was found in the urine and later there was intense glycosuria. In February, 1905, while the patient was in the hospital on the ordinary diet, the urine contained 2.63 to 4.76 per cent sugar, representing from 1220 to 3020 grains in twenty-four hours. With a strict diabetic diet, the excretion of sugar was still from 209 to 809 grains in one day. A year later glycosuria ceased spontaneously. Polyuria and polydipsia persisted unchanged. A similar case was reported by Scheuplein. A man who suffered dislocation

of a thoracic vertebra in a fall showed marked glycosuria and polyuria on the eleventh day after the accident. Glycosuria disappeared on the forty-third day but polyuria continued. Two years after the accident there were no symptoms of diabetes. Leudet described a patient with syphilis who had sudden onset of unconsciousness and paralysis of the muscles of the eye, accompanied by polyuria and glycosuria. Under treatment with potassium iodide the polyuria and glycosuria disappeared and the nervous symptoms were ameliorated. Later there was aggravation of nervous symptoms and polyuria returned but the urine was free from sugar. Necropsy showed that the choroid plexus was adherent to the left border of the calamus scriptorius and the brain substance was eroded.

In certain cases with the alleged combination of diabetes insipidus and diabetes mellitus postmortem examination revealed changes in the pancreas. Hoppe-Seyler mentioned a case of diabetes insipidus with transitory glycosuria in which marked fatty degeneration of the pancreas was also found. Teschemacher described polyuria for several weeks after an operation on a pancreatic cyst, followed eight years later by diabetes mellitus. Mann reported a case of death from carcinoma of the stomach infiltrating the pancreas, in which polyuria and then glycosuria occurred a few days before death. A case of Lauter and Hiller, in 1925, showed interstitial pancreatitis with apparent decrease in the number of islands of Langerhans, but no qualitative changes in their appearance. Glycosuria had appeared eighteen months before death. Polyuria had existed for six months eleven years previously. In all these cases there is some doubt that the polyuria indicated true diabetes insipidus.

The use of insulin in cases in which diabetes mellitus was associated with diabetes insipidus has been described in a few instances. A preliminary report on Case 1 in this paper was given by Steel, in 1927. In this case and in the cases reported by Gibson, Magers and Dulaney and by Sweeney the effect of insulin on glycosuria was not unusual. In Gibson's case, that of a woman aged sixty-nine years, the glycosuria was 2.3 per cent and the fasting blood sugar was 0.357 per cent in September, 1923. After control of glycosuria the output of urine was still abnormally high, and later it reached from 6 to 9 liters daily. In May, 1925, polyuria with 4 to 6 liters daily was still present. Glycosuria was controlled by dietary restriction and the temporary use of insulin. Sweeney's case was that of a man aged forty years who had had diabetes mellitus for more than six years; polyuria was present intermittently. After control of glycosuria the excretion of a large amount of urine continued, the daily output being about 12 liters. It was reduced by treatment with extracts of the pituitary gland. The case of Cipriani, Morrachini and Rotta presented the extraordinary combination of diabetes insipidus, diabetes mellitus, acromegaly, pituitary adenoma, goiter and sclerosis of the pancreas. This patient exhibited the phenomenon of resistance to insulin. Large doses were given (300 units in twenty-four hours) to check glycosuria. A case of di Gugli-

elmo in which there was diabetes mellitus, polyuria and a lesion of the pituitary gland was likewise refractory to treatment with diet and insulin. In the case described by Lauter and Hiller insulin was said to be ineffective but details of the treatment were not given. Resistance to insulin is a rare condition, which is seen in most marked degree in certain cases of bronze diabetes (1). The occurrence of cases of pituitary lesions is significant. A notable example was seen at The Mayo Clinic in which a patient with diabetes mellitus and acromegaly was refractory to insulin after an operation for goiter (29).

Gibson, Magers and Dulaney also reported the investigation of the glucose tolerance in a series of seven cases of diabetes insipidus. Besides the case of frank diabetes mellitus in five others the response was like that in mild diabetes. Rabinowitch reported low tolerance for sugar in the study of a single case.

Experimental data bearing on the association of diabetes insipidus and diabetes mellitus were presented by Allen in 1913. In the early experiments with piqûre, Claude Bernard discovered that puncture of a point in the floor of the fourth ventricle in the neighborhood of the sugar center would bring about polyuria without glycosuria. The increased secretion of urine was only temporary and, as Allen pointed out, was therefore not a true reproduction of diabetes insipidus just as piqûre glycosuria is not a true reproduction of diabetes mellitus. Polyuria without glycosuria following partial pancreatectomy has been described by several investigators, and Allen made the same observation in a few cases. Yet polyuria was seldom marked and disappeared in a short time. The specific gravity when reported was 1.010 or more. Allen concluded: "The facts are not yet sufficient to warrant a conclusion or hypothesis."

Among approximately 100 cases of diabetes insipidus seen at The Mayo Clinic since 1912, there have been two cases in which diabetes mellitus has coexisted and one case in which glycosuria was present previous to the onset of diabetes insipidus.

REPORT OF CASES

Case 1. A boy, aged fourteen years, was brought to The Mayo Clinic, September 1, 1927, because of polyuria and polydipsia, which had appeared three and a half years previously, and of recent loss of weight and strength. His previous health had been satisfactory except for a mild attack of influenza in 1907, measles in 1908, and whooping cough in 1923. At the end of December, 1923, he became ill with fever, headache and stupor. When he was examined elsewhere, two weeks after the onset of the illness, he was stuporous and irritable. He had slight rotary nystagmus, ptosis of the left upper eyelid, and double vision. About this time he began to complain of unusual thirst and voided large quantities of urine. He had had nocturnal enuresis until the age of nine years, and in recent years had been in the habit of urinating one to three times during the night. He had been accustomed to drinking a large amount of water since infancy but the polydipsia and polyuria were now abnormal. The patient's physician diagnosed epidemic encephalitis and diabetes insipidus. The fever gradually subsided, and the somnolence, ptosis and double vision disappeared in a few weeks. At intervals during the next three years, the boy had spells of irritability and mental confusion, sometimes accompanied

by fever. There was almost complete failure to grow but the weight increased rapidly from 80 to 100 pounds. The polyuria and polydipsia continued. The output of urine was reported by the parents to be from 8 to 12 liters daily. Tests made on many occasions showed absence of glycosuria. Three weeks before admission to the clinic there was sudden increase in polydipsia and polyuria, accompanied by rapid loss of weight and strength.

On examination at the clinic the breath had an odor of acetone; urinalysis showed the presence of acetone bodies and 2.2 per cent sugar. The reduction test was checked by fermentation. The blood sugar was 360 mgm. for each 100 cc. The boy appeared considerably underdeveloped, his apparent age being about eleven. He was intelligent but nervous. He seemed tired and weak. Although his weight had fallen to 83 pounds, he was still plump. His height was 4 feet, 10½ inches. The skin was dry. The thyroid gland was not palpable; the heart and lungs were normal; the bladder was distended. Examination of the nervous system was negative. The ocular fundi and the visual fields were normal. The genitalia were underdeveloped; the pubic hair and other secondary male sexual characteristics were lacking. The breasts seemed prominent. The Wassermann reaction of the blood was negative. On two occasions the erythrocytes numbered 3,960,000 and 4,200,000, the leukocytes 10,100 and 8,900, and the hemoglobin was 80 and 72 per cent (Dare). Roentgenograms of the thorax and head were negative. The urine was free from albumin and blood cells. The blood urea was normal. Determinations of the basal metabolic rate were —6, —17 and —15 per cent.

Treatment by diet and insulin was commenced at once. The diet contained an allowance of 70 gm. of carbohydrate, 50 gm. of protein and 205 gm. of fat. Twenty to thirty units of insulin were given daily. The excretion of sugar was at first 19.8 to 38.7 gm. a day. Blood sugar determinations were 258 and 228 mgm. for each 100 cc. The insulin was given twice daily, and twelve days after admission glycosuria disappeared and the fasting blood sugar fluctuated between 121 and 143 mgm. for each 100 cc.

With the disappearance of glycosuria the patient improved in strength and vitality. He complained less of thirst but he continued to excrete from 6,050 to 9,800 cc. of urine daily. The specific gravity was 1.002 to 1.005. Hypodermic injection of pituitary extract twice in twenty-four hours reduced the excretion of urine to 1,850 cc. and abolished thirst. The administration of pituitary extract intranasally had no appreciable effect. The injection of pituitrin had no apparent effect on the blood sugar and did not interfere with the action of insulin, as is shown in Table 1. The clinical diagnosis was diabetes insipidus, hypopituitarism of the Fröhlich type and diabetes mellitus. The existence of true diabetes was shown by the association of glycosuria with marked hyperglycemia and ketosis. The response to treatment was not unusual in any respect. The

TABLE 1

COMPARISON OF EFFECT OF INJECTION OF INSULIN AND PITUITARY EXTRACT AND OF INSULIN ALONE

*Material Injected	Date, 1927	Blood Sugar		Urine		
		Time	Per Cent	Period	Volume, c.c.	
					In Period	Each Hour
10 units of insulin and 0.5 c.c. surgical pituitrin.	9–20	Before breakfast	0.121	1.5 hours before breakfast	200	133
		1 hour after breakfast	0.116	3 hours after breakfast	150	50
		2 hours after breakfast	0.125	Remainder of day	2550	131
		3 hours after breakfast	0.081			
10 units of insulin.	9–21	Before breakfast	0.143	1.5 hours before breakfast	525	350
		1 hour after breakfast	0.131	3 hours after breakfast	800	266
		2 hours after breakfast	0.114	Remainder of day	5675	291
		3 hours after breakfast	0.078			

*After specimen taken for determination of blood sugar and before breakfast.

parents were trained in home management of diet and insulin and the patient was dismissed September 3. He was feeling well and had regained 5 pounds in weight. Ten units of insulin were used twice daily to control diabetes mellitus. Diabetes insipidus was controlled by 0.5 cc. of pituitrin twice daily.

One month after the patient had returned home, the dosage of insulin was reduced because of hypoglycemic symptoms and finally insulin was omitted entirely. The urine remained free from sugar. Later less care was taken with regard to diet and as the urine still remained free from sugar, dieting was practically discontinued during the winter of 1928. Glycosuria returned in September, 1928. Since then dietary restriction has been carried on and insulin has been used. Ten units of insulin are given daily, and the urine is almost free from sugar. The pituitary treatment was discontinued about a month after the patient's dismissal because the injections were painful. The polyuria continued as before, the amount of urine varying somewhat from time to time. The patient has not grown or developed sexually. His weight has increased to 98 pounds. He feels well, and is making satisfactory progress in high school.

Case 2. A man, aged thirty-three years, came to The Mayo Clinic, May 2, 1929, complaining of polyuria and loss of weight. He had had diphtheria and scarlet fever in childhood, influenza at the age of twenty-two years and pneumonia at the age of twenty-four. The family history was not significant except that many of his relatives were obese. At the age of six years he had a fall which resulted in a wound of his hand. After this accident he began to complain of unusual thirst and excessive urination. Polydipsia and polyuria continued without much variation throughout childhood and into adult life. He usually drank from 20 to 30 liters of water each day and night. In spite of the severity of these symptoms he was able to work regularly, and to lead a fairly normal life. Treatment with pituitary extract two years before examination caused thirst and polyuria to disappear, but because it caused unpleasant symptoms and it was not convenient to take the injections were not continued. The patient was obese throughout childhood, and his weight increased to 230 pounds when he reached maturity. His height was only 5 feet, ½ inch. Physical development was otherwise satisfactory and sexual function was normal. He was always mentally alert and had led his class in school. His appetite was excessive and he had an abnormal craving for sweets. From the age of eighteen years he had been in the habit of eating at least a pound of candy a day.

Ten months before the patient's registration he had begun to lose weight and energy. Examination of the urine revealed glycosuria. A test made two years before and many earlier tests had been negative. Dietary restriction was advised, but was neglected. He was unable to give up candy. His weight decreased almost 60 pounds. He finally became alarmed about his condition and began to restrict his diet about two and a half months before admission. He avoided candy and sugar, and limited his intake of starchy foods. Glycosuria diminished, and the urine was free from sugar part of the time.

General examination showed nothing abnormal except extreme obesity. Examination of the eyes and nervous system was negative. The genital organs were well developed. The blood pressure was 110 systolic and 80 diastolic. The Wassermann reaction of the blood was negative. The basal metabolic rate was —3 per cent. A roentgenogram of the head did not show abnormality in the sella turcica. A single specimen of urine was free from sugar. The fasting blood sugar was 170 mgm. for each 100 cc. The results of a glucose tolerance test are shown in Table 2.

TABLE 2

GLUCOSE TOLERANCE TEST (100 GM. GLUCOSE)

	Blood Sugar, mg. for Each	Sugar in Urine	
	100 c.c.	Per Cent	Grams
Fasting	176	++	
After Glucose—½ hour	316	0.51	1.50
2 hours	448	1.03	2.88
3 hours	412	1.03	2.44

The clinical diagnosis was diabetes insipidus and mild diabetes mellitus. The patient was unable to remain for more complete observation or treatment. He was advised to continue careful dietary restriction, and the intranasal administration of pituitrin was suggested for the control of polyuria. A report from his physician, May 1, 1930, stated that his condition was about the same. The volume of urine was approximately 20 liters a day. Glycosuria was found at times when dieting was not strict enough. The patient's general health was fairly good, and his weight was unchanged.

Case 3. A woman, aged thirty-three years, came to The Mayo Clinic, May 23, 1929, because of lethargy and excessive thirst. Three years before this, hysterectomy had been performed because of a tumor of the uterus and at the time of the operation glycosuria was discovered. The diet was restricted for six days. She was then told that the excretion of sugar had ceased, and that dietary restriction need not be continued. Further information regarding her condition at that time was not obtained. Tests of the urine made one and a half years previously and numerous tests made during the year before examination disclosed absence of sugar. One year before examination, the patient had bumped her head against the top of an automobile. Soon afterward she had a febrile illness which lasted for a week; she began to complain of extreme thirst, and from that time was obliged to drink about 8 liters of water each day. For five months she had felt drowsy and weak, and her weight had gradually increased about 20 pounds.

General examination disclosed obesity, and slight puffiness of the face. The patient was weak and lethargic. While under observation in hospital she had fever irregularly, the afternoon temperature sometimes reaching 101° F. The output of urine measured from 3.5 to 7.2 liters in one day. The specific gravity was 1.002 to 1.003. A small amount of albumin was noted on one occasion but other tests were negative. The urine was free from sugar and the fasting blood sugar was 70 and 83 mgm. for each 100 cc. The Wassermann reactions of the blood and spinal fluid were negative. The spinal fluid contained 6 cells in 1 cubic millimeter. A roentgenogram of the head was negative. The basal metabolic rate was normal on two occasions.

The diagnosis was encephalitis with secondary diabetes insipidus. The administration of pituitary extract temporarily abolished thirst and reduced the output of urine to normal. Diabetes insipidus was, however, a minor disturbance in this case. Death occurred from encephalitis six months later.

The glycosuria which occurred three years previous to examination was probably nondiabetic. A glucose tolerance test might have revealed latent diabetes mellitus, but since the patient was seriously ill, examinations and tests which were not essential were avoided. In any case, there was no apparent connection between the polyuria and glycosuria, since the former was secondary to encephalitis and the latter had been observed on only one occasion two years prior to this illness.

COMMENT

In Cases 1 and 2 the diagnosis of diabetes mellitus is well established. Glycosuria was accompanied by marked hyperglycemia and in one case by ketosis. In both cases there was rapid loss of weight. The diagnosis of diabetes insipidus is equally certain. In Case 1 it was secondary to encephalitis and was accompanied by signs of hypopituitarism: failure of growth, genital hypoplasia, obesity and subnormal metabolic rate. In Case 2 there was no definite evidence of intracranial lesion, but the obesity suggested underactivity of the pituitary gland.

The total number of authentic cases of the association of diabetes insipidus and diabetes mellitus is not large, and perhaps no greater than would result from pure coincidence. Yet it is interesting to consider the possibility of an intimate relationship. The clinical behavior of diabetes mellitus in certain of the cases under consideration is so extraordinary that it suggests the operation of some unusual factor. Such fluctuations in tol-

erance as were observed in Case 1 reported here and in cases described by French and Ticehurst, Teschemacher, Scheuplein and Leudet are seldom encountered in ordinary diabetes. The apparent recovery of a child from diabetes is extremely rare. The history of encephalitis or of injury to the head in many of these cases suggests that diabetes may be of central origin. If such a diagnosis is ever justified, it would seem applicable under these circumstances. The same intracranial lesion may be responsible for both polyuria and glycosuria.

The occurrence of pancreatic lesions in a few cases of diabetes insipidus and the appearance of polyuria after partial pancreatectomy led to the suspicion that both diabetes mellitus and diabetes insipidus might be of pancreatic origin. In the light of modern knowledge the attempt to attribute both diseases to a pancreatic lesion is unjustified. When polyuria follows partial pancreatectomy, it is of brief duration, and that observed in the cases reported with pancreatic lesions has likewise been of uncertain type. This polyuria may perhaps be due to disturbance of the sympathetic nerves in the region of the pancreas.

Cases 1 and 2 reported here showed presumptive evidence of hypopituitarism. The relationship of the pituitary gland to carbohydrate metabolism is unsettled. It is well known that hyperpituitarism as manifested by acromegaly is commonly associated with low tolerance for sugar. A high tolerance for sugar was considered by Cushing to be characteristic of hypopituitarism. Engelbach reported that in hyposecretion of the posterior lobe he found increased tolerance in 91.4 per cent of cases but decreased tolerance in 8.6 per cent; in hyposecretion of the anterior lobe he reported increased tolerance in 71.5 per cent and decreased tolerance in 28.5 per cent. John described five cases of hypopituitarism in which he found decreased tolerance for sugar. One case was of definite diabetes, another was of mild diabetes, and three patients were in a prediabetic state. It is evident that the problem is very complex. Pituitary extract has an antagonistic action toward insulin in its effect on the blood sugar of rabbits. Fortunately it did not interfere appreciably with the treatment by insulin.

Whether or not diabetes mellitus is due to pancreatic insufficiency primarily or to inhibition of the pancreas by the central nervous system or by the pituitary gland, response to treatment by insulin is the same, with rare exceptions. In the cases of Gibson and Sweeney and in Case 1 reported here, glycosuria was controlled by insulin in the usual way.

SUMMARY

Two cases are described in which diabetes insipidus was associated with diabetes mellitus and one case in which transitory glycosuria preceded diabetes insipidus. The relationship of these two diseases is still uncertain. The three cases are presented in the hope that the accumulation of more information may help to solve the problem. From the prac-

tical standpoint it is significant to find that the disturbance of carbohydrate metabolism encountered in these cases can usually be controlled by diet and insulin, and the use of pituitary extract for control of polyuria does not interfere with the effectiveness of insulin.

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THE RESERVE INCRETORY CAPACITY OF THE PANCREAS

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In a recent work we have set forth the fundamental features of a new method devised for the investigation of the "reserve functional capacity of the pancreas." We have shown for the first time that the subcutaneous or intravenous injection of duodenal secretin causes a fall in the blood sugar. This occurs in either normal men or experimental animals and the hypoglycemia thus produced results from an activation of the secretion of the islands of Langerhans.

The reserve capacity of the normal pancreas can be represented quantitatively as the equivalent of 450 units of insulin. The amount of insulin required for the utilization of a normal carbohydrate ration of 500 grams is approximately 250 units, assuming, that, in round numbers, each two grams of sugar requires one unit. According to the experimental results of Woodyatt, Sansum and Wilder, the glucose tolerance of the healthy individual is 0.80 to 0.90 (approximately 0.85 grams per kgm. per hour). Accordingly, the quantity of glucose theoretically utilizable per day would be 0.85 x 24 (hours) x 70 (kgm.) or approximately 1400 grams. This would require the activity of about 700 units of insulin, hence, under ordinary conditions of alimentation the "reserve capacity" of the pancreas would be 700 minus 250 equals 450 units, i. e., approximately twice the amount secreted under ordinary conditions. Indeed, it has been discovered that the pancreas of the diabetic subject has a certain reserve secretory capacity. If one determines the carbohydrate tolerance in a given diabetic and then demonstrates an increased tolerance after the injection of duodenal secretin it follows that the subject must have had a certain amount of reserve tolerance that was not called forth by the administration of carbohydrate alone.

Without consideration of the different means of evaluating the secretory capacity of the pancreas (tests of Döpisch and Hassenörhle, based on Staub, etc.) we shall discuss directly the fundamentals of the method we propose. Studying the behavior of the blood sugar following the injection of secretin, we can note the reserve secretory capacity of the pancreas since, while the totally insufficient gland does not respond with diminished blood sugar to such injections, the partially insufficient pancreas reacts with a greater secretion of insulin producing varying degrees of hypoglycemia. However, it must be admitted that in certain cases also which we cannot consider as serious, it can be observed at times that the

injection of secretin does not depress the level of the blood sugar. This appears to be attributable to the fact that there is no exact parallelism between the degree of overt pancreatic insufficiency and the reserve capacity which the organ possesses.

Thus, theoretically, the following cases must be considered:

(1) Total pancreatic exhaustion with lack of reaction to secretin; (2) Relative pancreatic deficiency, with little or no reserve capacity; (3) Pancreatic insufficiency with good reserve capacity.

The insufficient pancreas which possesses a certain reserve capacity responds to duodenal secretin injection with a noticeable descent of blood sugar, while the gland which does not have reserve capacity does not react to the stimulus of the secretin with a secretion of insulin. According to this conception the only thing that the secretin tests show us is the amount of the *reserve* capacity of the insufficient pancreas. That there is not necessarily any parallelism between the degree of insufficiency and the actual reserve capacity, an examination of the following tables shows.

TABLE I

GLYCOSURIC EFFECT OF INCREASING AMOUNTS OF CARBOHYDRATE IN TWO DIABETICS

I		II	
Input (Grams)	Output (Grams)	Input (Grams)	Output (Grams)
50	0.	30	0.
50	0.	50	3.80
100	2.25	70	5.0
150	2.80	100	12.25
200	10.0		
250	15.30		

Subject II had a lesser *tolerance* since he showed a glycosuria of 3.80 grams with the ingestion of 50 grams of carbohydrate, whereas Subject I excreted no glucose with 50 grams ingestion and customarily eliminates 2.25 grams with the addition of 100 grams per day. When the ingested carbohydrate was doubled in amount, Patient I put out four and a half times more sugar, while Patient II lost little more than double the original amount. This must be interpreted to mean that the reserve capacity of Patient II was greater than that of No. I in spite of a higher degree of initial overt insufficiency.

In the accompanying table are the results obtained with tests of secretin on diabetic patients. Occasionally the test has been repeated on the same patient on different days. In general the injection of secretin has proved to be effective in almost all the patients examined. Nevertheless, there can be noticed an exceptional rising content which falls later below the initial fasting level. The usual thing is that the blood sugar falls in the course of the first hours; but as we have already indicated, there are cases in which variations in the sugar content are hardly produced during the whole duration of the test. The data gathered permit

TABLE II

SECRETIN TESTS IN THIRTEEN PATIENTS

Case	Secretin Injected (cc.)	Fasting Blood Sugar Level	After ½ Hour	After 1 Hour	After 1½ Hours	After 2 Hours
I	2	2.07	1.07	1.10	1.01	....
	2	2.10	1.92	1.10	1.04	1.00
II	1	1.09	0.96	0.94	0.90	0.81
	1	1.04	0.98	0.96	0.94	0.87
	1	0.92	0.80	0.85	0.80	....
	1	3.02	3.01	2.93	2.40	....
	1	0.84	0.62	0.56	0.45	0.38
III	1	2.67	2.41	2.39	2.33	2.28
	1	2.36	2.32	2.00	2.05	1.99
IV	1	1.26	1.13	1.22	1.32	1.25
V	1	1.26	1.45	1.53	1.37	1.24
	1	1.40	1.33	1.42	1.31	1.16
VI	1.5	2.82	2.67	2.53	2.10	2.01
VII	1	2.70	2.50	2.38	2.36	2.50
VIII	2	2.11	2.10	2.24	2.30	1.11
	2.5	1.98	1.90	1.88	1.96	1.76
	2.5	2.10	2.16	2.50	2.00	2.07
IX	1	2.05	2.01	1.98	1.97	1.70
	2.5	1.74	1.68	1.80	1.52	1.40
X	1	1.95	1.61	1.75	1.81	1.88
XI	2	1.18	0.90	0.87	0.80	0.76
XII	1	2.29	2.29	2.02	1.94	1.62
XIII	1	3.10	3.08	3.10	....	3.15

advancing the statement that those subjects who do not react to the injection of secretin with hypoglycemia represent precisely the serious cases, and partly, cases which without deserving the qualification serious, are characterized by low reserve capacity.

In so far as the influence of the secretin on the elimination of sugar is concerned, we have gathered some observations. In general terms, the sugar content diminishes in the urine collected during the test in accordance with the data of Table III.

TABLE III

Case	Sugar Output per Liter—Control (grams)	During the Test (grams)
I	28.68	.17
II	2.30	1.95
III	32.50	28.93
VIII	13.90	2.90
	1.80	1.50
IX	14.50	2.80
XI	10.	9.

The results obtained in the treatment of diabetes with secretin will be the subject of a later publication.

SUMMARY

The injection of duodenal secretin has been shown in a series of human cases ordinarily to decrease the blood sugar level or glycosuria, hence to stimulate the islands of Langerhans. The amount of this decrease has no necessary correlation with the actual overt reaction to carbohydrate ingestion per se. The amount of reduction following the administration of a standard dose of secretin serves as a criterion of the *reserve capacity* of the islands of Langerhans.

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SEXUAL DYSFUNCTION IN ADENOMAS OF THE PITUITARY BODY

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For the past two decades it has been customary to subdivide pituitary disorders, as the more simple thyroid disorders are satisfactorily subdivided, into two opposed groups, those due to glandular oversecretion (hyperpituitarism) in which overgrowth is the striking clinical feature, and those due to glandular underaction (hypopituitarism) characterized by adiposity and genital dystrophy and also by dwarfism when the process starts early in life.

This simple conception has been temporarily useful as a working basis, but the recent disclosures that the anterior pituitary contains two chemically separable hormones, one activating growth and the other the reproductive functions, serves not only to clarify much that was obscure in the hyper- and hypo-pituitary syndromes but obliges us to modify our former views regarding them. It now becomes evident that clinical states due to excessive or diminished activity of the growth hormones, and states due to excessive or diminished activity of the sex hormone, will come to be clinically recognizable. It has long been difficult to understand why sexual dysfunction, particularly evident as amenorrhoea in women, should accompany both hyper- and hypo-pituitary states as they are encountered in the clinic.

It is not definitely known whether the acidophilic and the basophilic cells represent different stages in the activity of one and the same element, as Rémy-Collin (1) strongly believes, or whether they are cells of a fixed type as others have assumed, but numerous observations, both clinical and experimental, indicate that the acidophilic elements elaborate the hormone of growth, and it would appear from the studies of P. E. Smith (2), of Van Wagenen (3), and of Engel (4), that the basophilic cells elaborate the sex hormone. Experimental evidence regarding the dual hormones has been recently assembled by Teel and Cushing (5).

The adenomas of the anterior pituitary are of two principal types, both of which, with but few exceptions, occur in adult life. The more common type known as a chromophobe adenoma is composed of non-granular cells which, so far as is known, have no secretory activity; the less common type, that associated with acromegaly, as shown by Dott and Bailey (6), and Bailey and Cushing (7), is invariably composed of acidophilic elements. Adenomas of both of these varieties usually come to distend the sella turcica and many of them ultimately reach a sufficiently large size to implicate the optic chiasm, and because of the resultant impairment of sight patients victimised by these tumours frequent neurosurgical clinics.

Still another type of adenoma, which apparently never attains a large size, is composed of basophilic cells, and although it has heretofore been looked upon merely as a pathological curiosity, our recently acquired knowledge of the relation of the basophilic elements to the functions of sex has drawn renewed attention to adenomas of this variety. Teel (personal communication), has encountered a case in which the presence of one of these small basophilic adenomas, predicted during life, was disclosed at autopsy. Though these several isolated facts shed new light on the syndromes of the pituitary adenomas in general, they leave unexplained why it is that sexual dystrophy should accompany the two more common types, acidophilic and chromophobe, both of which may attain a large size.

The interest in this clinic in late years in what has been designated "the chiasmal syndrome" (8) (namely, primary optic atrophy with bitemporal hemianopsia in adult patients with an unexpanded sella turcica), has led to many exploratory exposures of the chiasmal region, in the course of which small suprasellar adenomas that have failed to expand the pituitary fossa have occasionally been encountered. These suprasellar adenomas have all been of the chromophobe type and the greater number of them in women, all of whom had continued to menstruate normally, whereas amenorrhoea was an inevitable accompaniment of adenomas of this same variety which had arisen within and had served greatly to expand the sella turcica.

This observation led Dr. Cushing to believe that the sexual dystrophy (notably shown as amenorrhoea in women) associated with chromophobe adenomas might be due to the inactivation of the basophilic cells from the effects of compression by an expanding lesion within the confines of the sella (Cf. Fig. 1). Could this be shown to be true, it might account for the fact that sexual dystrophy so often accompanies both of the common types of adenomas, acidophilic and chromophobe. The idea was further supported by the known fact that the acidophilic adenomas with acromegaly were apt to be of smaller size and were less likely to affect menstrual activity than the chromophobe adenomas.

It was in pursuance of this suggestion that the following study was undertaken. It concerns the degree of expansion of the sella turcica in relation to the disturbances of sexual function, in the complete series of pituitary adenomas, acidophile and chromophobe, admitted to the Peter Bent Brigham Hospital from 1913 to August 1, 1930—a total of 367 cases. Acromegaly is so unmistakable that patients in whom the tumour has been histologically verified at operation and those in whom operation has been withheld have been grouped together. In patients with chromophobe adenomas, only those in whom the lesion has been histologically verified are incorporated in the study.

Since the presence or absence of the regular menstrual cycle in the female provides a reasonably accurate indication of the functional activity of the reproductive organs, any disturbance of the normal cycle, whether due directly to ovarian disease or indirectly to pituitary disease, is at once

brought to the notice of the patient. Consequently, more dependable data on sexual dysfunction in pituitary disease are provided by women than by men.

(1) SEXUAL DYSFUNCTION IN THE FEMALE

Explanatory Basis of Study. In checking the sex history of women with pituitary adenomas it has been found convenient to divide the disturbances of menstruation into several groups, *viz.:* (1) Patients in whom normal menstruation was uninterrupted up to the date of admission to the hospital, even in spite of the presence of well-marked signs of pituitary

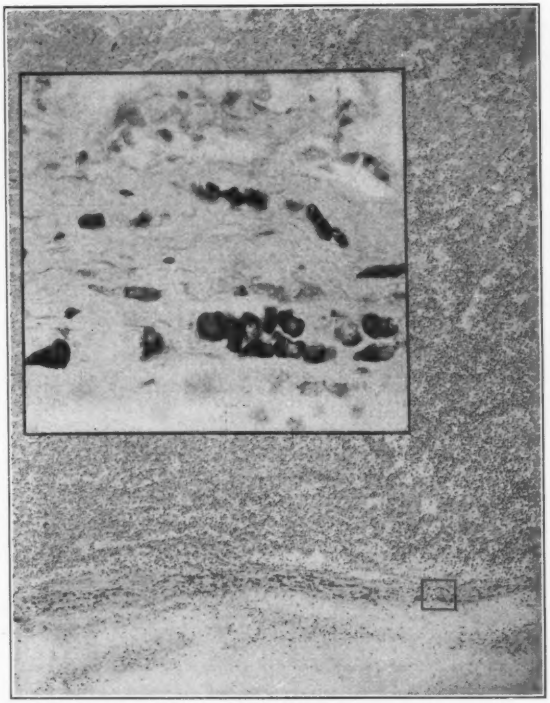

Fig. 1. Margin of large pituitary chromophobe adenoma, x 50, to show manner of compression of peripheral cells by expanding adenoma. Insert shows granular cells from squared area on higher magnification (x 600).

disease; (2) Patients in whom menstruation though still present had, since the onset of the disease, become irregular, usually with prolongation of the interval to two to three months; (3) Patients in whom menstruation continued regularly for a time, perhaps for several years, after the appearance of the disease, but subsequently ceased, so that there was definite "post-symptomatic" amenorrhoea on admission to the hospital; (4) Patients in whom the amenorrhoea coincided with the appearance of the other symptoms, the disorder in many instances having become apparent during a

pregnancy after which menstruation had never been resumed; and (5) Patients in whom the amenorrhoea preceded the appearance of other symptoms—"presymptomatic" amenorrhoea.

Not infrequently in addition to the abnormal menstruation a decrease or loss of libido is recorded, but this is a subjective phenomenon and information concerning it is less likely to be volunteered and is not always enquired into.

On the basis of the X-ray films it has been found convenient to divide the cases into three groups: (1) Those in which the pituitary fossa is approximately of normal size or shows only slight enlargement; (2) Those in which it shows a medium enlargement; and (3) Those in which the sella is widely expanded or completely wiped out. The sella accordingly will hereafter be referred to as small, medium, or large.

(a) *The Chromophile Adenomas.* Even a small chromophile adenoma makes its presence quickly known by the unmistakable appearance of acromegaly, so that the time of onset of the disease is usually determinable with some accuracy. For the purpose of the present study this group of acromegalic females is the most satisfactory one because both the time of onset of the disease and the amenorrhoea can be established with reasonable exactitude. The 73 cases are arranged in accordance with the above-mentioned programme in the accompanying table (Table I).

TABLE I
ACROMEGALY IN THE FEMALE

Menstruation	Size of Sella			Total
	Small	Medium	Large	
1. Uninterrupted Menstruation	10	6	0	16
2. Menstrual Irregularity	3	2	1	6
3. Post-acromegalic Amenorrhoea	2	16	5	23
4. Coincidental Amenorrhoea	2	5	6	13
5. Pre-symptomatic Amenorrhoea	1	4	3	8
	18	33	15	66
Not tabulated (onset after natural or artificial menopause)	4	2	1	7
	22	35	16	73

From this table it can be seen that there is a gradual transition from the cases with normal menstruation and a small sella to those with complete amenorrhoea and a large sella. Attention may be drawn to the following points: (1) That 10 of the patients with normal uninterrupted menstruation had a small and 6 a medium sella, whereas none had a large sella; (2) That approximately one-half (16) of the large group of patients with a medium-sized sella, though amenorrhoeic on admission, had continued to menstruate normally for a time after the disease was manifest; (3) That all except one of the patients with a large sella had ceased to menstruate. In illustration of the ten cases with a small sella and continued normal menstruation the following example may be given.

CASE I. (Surgical No. 27528.) *Progressive acromegaly for 14 years, together with normal menstruation and a small sella. No failure of vision or other neighbourhood signs.*

History. A 33-year-old unmarried woman entered the hospital on October 29, 1926, complaining of slight headaches. Indications of acromegaly were first noticed when she was 19 years of age and the disorder had steadily progressed. For four years she had had occasional slight headache. Vision was unimpaired.

Menstrual history. Menstruation began at twelve years of age and the periods were still regular at the time of admission.

Physical examination. The patient presented all the characteristic appearances of acromegaly—prognathism, coarsening of features, enlargement of the extremities, excessive perspiration, hypertrichosis. The ophthalmological examination revealed normal visual acuity, normal fundi and normal fields. The cranial roentgenograms (Fig. 2) showed only a very slight possible expansion of the sella turcica.

There were no indications for operation. In spite of a slight progress in her acromegaly she was continuing to menstruate with perfect regularity when she last reported in November of 1929.

Fig. 2. (Case I.) The essentially normal sella (nat. size) of an acromegalic with a small intrasellar adenoma.

With a comparatively small sella and the absence of any evidence of chiasmal pressure, it may be assumed that the intrasellar pressure in this case had not been sufficiently raised to disturb the function of the basophilic elements.

The following case illustrates the group of 16 patients who had continued to menstruate normally for a time after the acromegaly became apparent.

CASE II. (Surgical No. 36036.) *Progressive acromegaly of seven years' duration. Normal menstruation for 3½ years followed by irregularity and final cessation. The sella showed a medium enlargement.*

History. Miss Leah D., 38 years of age, was admitted on March 17, 1930, with the chief complaint of headaches. Seven years before admission her attention was first drawn to a steadily progressive increase in the size of her hands

and feet and a general coarsening of her features. For three and one-half years she had been having increasingly severe temporal headaches. During the last two years a slight blurring of vision was noticed but this was never a prominent symptom.

Menstrual history. Menstruation commenced at 14 years of age and continued without interruption until three and a half years before admission when the interval lengthened out to six or eight weeks and the flow became much more profuse. After six months of irregularity and six months of amenorrhoea a very profuse period occurred which lasted for two weeks. Since that time, for two and a half years, amenorrhoea has been complete, though the patient's libido was said to have remained meanwhile unaffected.

Physical Examination revealed all the typical features of advanced acromegaly. Ophthalmoscopic examination showed a slight early primary optic atrophy. Perimetry disclosed merely an upper bitemporal notching with a slight lowering of visual acuity. The cranial roentgenograms (Fig. 3) showed a medium enlargement of the sella. The patient had been having prolonged radiotherapy which apparently had arrested the activity of the malady. Surgical intervention was not indicated.

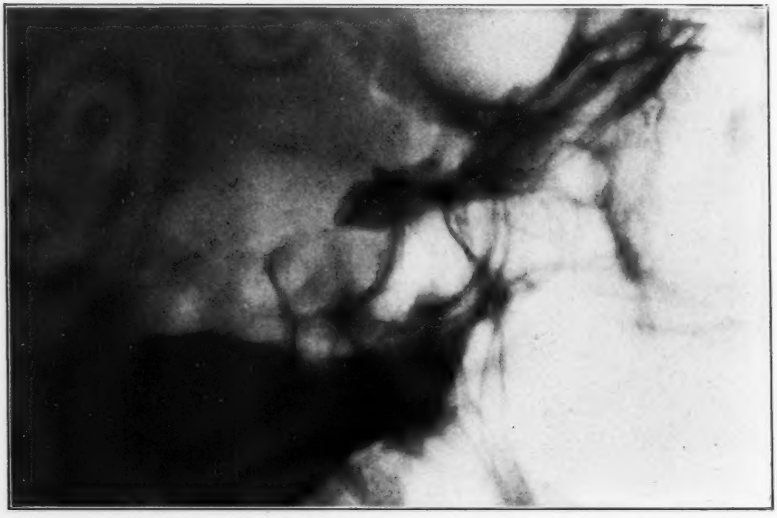

Fig. 3. (Case II.) Showing (nat. size) a medium expansion of the sella.

This case represents the large group with post-symptomatic amenorrhoea and a medium sella. Had the patient been seen four years earlier, she might then have had a small sella and have been placed in the same category as Case I. The major signs and symptoms of acromegaly in women appear in the following order: (1) Pathological overgrowth when the sella may still be small; (2) amenorrhoea by which time a moderate enlargement of the sella may be expected; and (3) chiasmal symptoms shown by visual field defects, the sella being usually greatly expanded.

(b) *The Chromophobe Adenomas.* Since these tumours call forth a clinical syndrome far less striking than that of acromegaly, the time of onset of the disease is less easily determined. The following table will show that amenorrhoea is usually premonitory, but the symptom which almost

invariably prompts the patient to seek advice, and which therefore is arbitrarily used in this study as "primary," is the onset of failing vision. This, however, under ordinary circumstances is quite a late symptom, for a pituitary adenoma must necessarily have attained considerable size before it comes to press against the chiasm. Notable exceptions to this rule occur in the small but well-defined group of suprasellar adenomas in which the sella is not enlarged and in which menstruation remains unaffected.

In many cases headache, ocular pain, obesity, or other symptoms precede the onset of eye signs, but they are often absent or too indefinite to be used as a basis for comparing the time of onset in the different cases. Because of the frequent absence of any striking and characteristic external appearance such as betrays the presence of the adenoma of acromegaly, only the chromophobe adenomas which have been histologically verified have been included in this series. Particularly in the absence of an expanded sella, the clinical signs may so closely simulate other lesions, such as glioma of the optic chiasm, aneurysm and suprasellar meningioma, as to make the clinical diagnosis uncertain.

TABLE II
CHROMOPHOBE ADENOMA IN THE FEMALE

Menstruation	Size of Sella			Total
	Small	Medium	Large	
1. Uninterrupted Menstruation	3	0	0	3
2. Menstrual Irregularity	2	3	1	6
3. Post-symptomatic Amenorrhoea	0	2	2	4
4. Coincidental Amenorrhoea	0	2	1	3
5. Pre-symptomatic Amenorrhoea	3	26	34	63
	8	33	38	79
Not tabulated (onset after natural or artificial menopause)	1	5	8	14
	9	38	46	93

The table shows that in 63 out of 79 women (*circa* 80 per cent) with chromophobe adenomas, amenorrhoea has long preceded the onset of eye signs and the several cases in which early gynaecological explorations had been made might justifiably be added to increase the percentage. The nine patients with normal or only irregular menstruation, with a single exception, have been shown to have suprasellar adenomas with early eye signs.

Particular attention may be drawn to the following points: (1) That 50 per cent of these patients had a large and only 10 a small sella, whereas in acromegaly (Cf. Table I) only 22 per cent had a large and 30 per cent a small sella; (2) That only about 4 per cent of the patients had uninterrupted menstruation in contrast to 24 per cent in acromegaly; (3) That the majority of cases in which, to judge from the expanded sella, the growth was therein confined, had amenorrhoea as the first symptom; (4) That in only a small group (4 cases) did amenorrhoea occur secondary to the appearance of eye signs (i.e., "post-symptomatic"), the enlarged sella

of these cases being probably ascribable to the secondary intrasellar invasion of an adenoma which was largely suprasellar at the outset. The following case is an example of the large group of chromophobe adenomas in which amenorrhoea is the premonitory sign.

CASE III. (Surgical No. 35865.) *Sudden onset of amenorrhoea 1½ years antecedent to progressive failure of vision. Partial extirpation of adenoma with recovery of vision but persistent amenorrhoea.*

History. Doris C., unmarried, 23 years of age, was admitted on February 19, 1930, with the complaint of failing vision. Her menstruation, which commenced at 12 years of age, had been regular for eight years when in 1927 it suddenly ceased. Eighteen months later she accidentally noticed a blurring of sight in the right eye. Since then there had been a progressive failure of vision in this eye without any marked subjective involvement of the left eye. Coincident with the onset of amenorrhoea she began to have occasional slight vertical headaches which for 18 months past had been severe and were accompanied by pain in the region of the right eye. In 1928 she commenced to gain weight rather rapidly and since then had gained about 16 pounds.

Physical examination. Apart from the examination of the eyes, this was essentially negative. Ophthalmoscopic examination revealed a moderate primary atrophy on the right and a normal fundus on the left. The perimetric fields showed a nearly complete temporal hemianopsia on the right, with a marked lowering of the visual acuity, and a beginning upper temporal defect on the left. The sella was large (Fig. 4).

On March 6, 1930, a right transfrontal exploration disclosed a large adenoma extending to the right of the pituitary fossa under the right optic nerve. The tumour was thoroughly excavated. She made a good recovery with complete return of vision to normal, but there has been no return of menstruation.

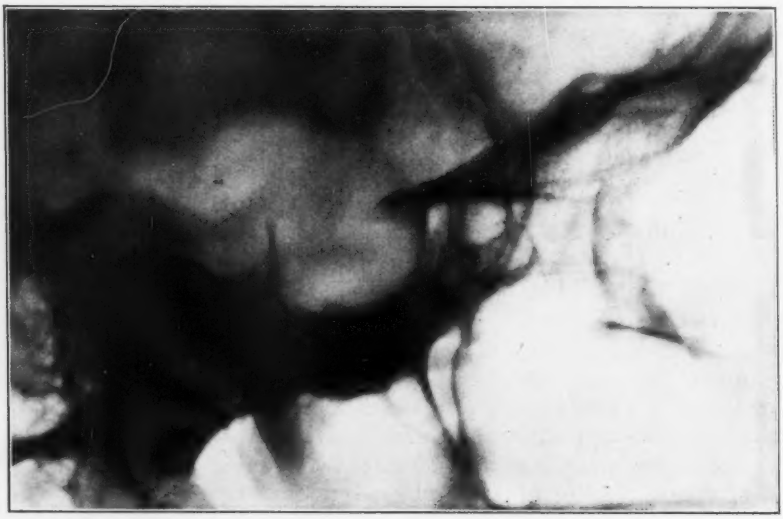

Fig. 4. (Case III.) A sella which has become widely ballooned by a large intrasellar chromophobe adenoma (nat. size).

This is a fairly typical history of an intrasellar chromophobe adenoma, though the patient is rather young, the average age for lesions of this type being 39 years. Chromophobe adenomas, however, are occasionally met with in childhood. The youngest case in the series is a girl of 9, and there

are several cases in which evidence of a pituitary adenoma (failing vision, obesity, etc.), occurred in the late 'teens. These patients naturally have never menstruated and the genital organs have remained infantile. They have been grouped as cases of pre-symptomatic amenorrhoea.

In the average case, the first sign is amenorrhoea to which little serious attention is given and for which various ovarian or multiglandular extracts are frequently prescribed. Then after a period of even five or ten years, according to the rapidity of the tumour's growth, vision becomes impaired and glasses are tried, but without any relief. Finally a primary optic atrophy or bitemporal field defects reveal the true nature of the condition and cranial roentgenograms show the characteristic ballooning of an intrasellar adenoma. Had roentgenograms been taken in these cases after the onset of the amenorrhoea, but before the subjective loss of vision, they would almost certainly have shown an enlargement of the pituitary fossa.

Fig. 5. (Case IV.) The small sella of a patient with a suprasellar adenoma showing the sharpened anterior and eroded posterior clinoids (nat. size).

The following is an example of the group of chromophobe adenomas which fail to expand the sella and in which normal menstruation is retained.

CASE IV. (Surgical No. 22668.) *Progressive bitemporal field defects with normal menstruation and a small sella. Transfrontal exploration with removal of suprasellar adenoma.*

History. Nora McA., an unmarried woman of 45 years, was admitted on November 25, 1924. Eleven months previously, she noticed haziness of sight in the temporal field of the right eye and five months later a similar defect in the left eye. There had been a drawing pain behind each eye but no headache.

Menstruation began at 16 and had been perfectly normal and regular all her life. There had, however, been no period during the two months immediately before admission.

Examination. The ophthalmological findings showed: (1) Bilateral primary atrophy more marked on the right; (2) Bitemporal field defects with 20/50 acuity on the left and 20/200 on the right. The sella (Fig. 5) was unexpanded though the anterior clinoids were sharpened. No suprasellar calcification was seen. The physical examination was otherwise quite negative.

The presence of bilateral primary atrophy, bitemporal hemianopsia and a normal sella in a woman of middle age without signs of hypopituitarism led to the diagnosis of suprasellar tumour, probably meningioma. The lapse of two recent periods was looked upon as indicating the probable onset of menopause.

Operation. A right transfrontal exploration disclosed a suprasellar adenoma which was radically extirpated. The menstrual periods returned immediately after operation and continued regularly for twelve months when they again ceased, presumably from the menopause.

This case belongs to the recently recognized and well defined group of suprasellar adenomas (Cf. Fig. 6), which extrude upward through a defective diaphragma sellae before the sella itself becomes expanded. The first symptom is that of chiasmal involvement, for which the patient immediately

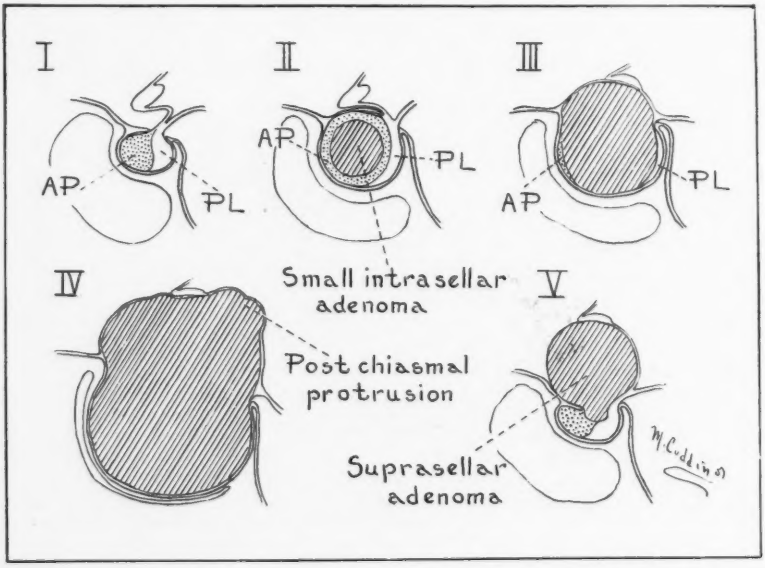

Fig. 6. A series of drawings to illustrate the mechanical effects of an expanding pituitary adenoma: (1) The normal pituitary gland and optic chiasm; (2) A small intrasellar adenoma with only a slight expansion of the sella; (3) A larger adenoma beginning to stretch the chiasm—a little anterior lobe still remains; (4) A widely expanded sella and greatly stretched chiasm; (5) A suprasellar adenoma which has implicated the chiasm without compressing the anterior lobe.

seeks advice, menstruation usually being still normal or only very slightly affected. Under these circumstances the tumour does not greatly flatten or compress the remainder of the anterior lobe whose chromophilic and basophilic elements may be assumed to retain their normal functional activity. The menstrual cycle consequently remains unaffected.

Pregnancy in the Presence of Pituitary Adenomas. Though normal menstruation, as we have seen, may continue after the onset of definite

signs of pituitary disease, there is a possibility that the reproductive apparatus might have become affected in some unknown way which would interfere with actual reproduction. It is of interest, therefore, to group together all the patients who became pregnant after the onset of the disease.

(a) *After the Onset of Acromegaly.* Of the 73 acromegalic females 7 had had early hysterectomy; 23 were unmarried; 12 were married but approaching the menopause, the last child having been born many years before the onset of the disease; and 12 had developed amenorrhoea soon after the onset of the disease. There remain 19 young married women who continued to menstruate after acromegaly was apparent, and in 6 of them (i.e., 32 per cent) a normal pregnancy occurred with full-time delivery, three of them having become pregnant twice.* The sella in two of these six women, when they came under observation, was small and normal menstruation still occurred; in the other four the sella was considerably enlarged and in each of them there had been no return of menstruation after childbearing. In two instances, after operation and sellar decompression, normal menstruation subsequently returned. In none of these six patients was there any evidence of chiasmal involvement, and had it not been for the unmistakable acromegaly the presence of the adenoma would have been unsuspected.

The following example may be given in illustration of the group of cases in which pregnancy occurred during the progress of the disease.

CASE V. (Surgical No. 1053.) *Progressive acromegaly of 7 years' duration beginning during pregnancy. Return of normal menstruation with two subsequent normal pregnancies, amenorrhoea following the last. Later development of eye signs. Medium enlargement of the sella.*

History. Josephine C., a 32-year-old married woman, was admitted on March 20, 1914, with the complaint of enlargement of the features, headaches, and recent failure of sight. She had been married 10 years and had given birth to three children, respectively 7, 5 and 2½ years of age. Her unmistakable acromegaly had first been recognized during the course of the first pregnancy and it had shown exacerbations during each succeeding one. The menstrual periods had always been regular (apart from the interruptions of child bearing) until after the birth of the youngest child, since when they had never been resumed. Since that time she had suffered more or less from frontal and bitemporal headaches and for the past six months there had been a progressive impairment of vision.

Examination. The patient presented the typical features of acromegaly. Ophthalmological examination revealed a clean-cut bitemporal hemianopsia and bilateral primary optic atrophy. The sella showed a medium enlargement (Fig. 7).

A transphenoidal operation with sella decompression and partial removal of the tumour was followed by considerable amelioration of her discomforts and improvement in vision.

This story is a fairly common one. That exacerbations of acromegalic symptoms may occur during successive pregnancies is well known, and in the terms of our present thesis it may be assumed that only when the adenoma during the last pregnancy reached a size sufficient to expand the sella widely were the basophilic elements so effectively compressed as to interfere with their secretory activity in starting the ovulatory cycle.

*H. B. Evans (J. A. M. A., 1928, **91**: p. 1337), has expressed the belief based on his experiences with experimental gigantism in the female rat that growth hormone is counteractive to the hormone of sex. This apparently does not apply to the human acromegalic.

(b) *After the Appearance of Eye Signs in Chromophobe Adenomas.* In the chromophobe cases, as already explained, it is difficult to determine the time of onset of the malady with any precision, amenorrhoea in the majority of instances being the primary symptom. Of the 10 examples in which permanent amenorrhoea immediately followed pregnancy none had headaches, failing vision, obesity, and so on before the pregnancy with the exception of one patient in whom eye signs had been present for two years. All of the five married women who continued to menstruate after the onset of eye signs had suprasellar adenomas with a small sella, and one of them became pregnant in the course of the disease. It is quite probable that in the other cases the supervention of pregnancy served to accelerate the growth of a pre-existent symptomless adenoma which grew sufficiently large to compress the basophilic elements and cause the permanent amenorrhoea.

Fig. 7. (Case V.) To show the outline (reinforced on a print from an old glass negative) of a medium sella in an acromegalic patient (nat. size).

Post-operative Return of Menstruation. If our assumption is correct that the interruption of the menstrual cycle associated with chromophile and chromophobe adenomas alike is due to nothing more than compression of the basophilic elements by the progressive enlargement of the adenoma, then any return of menstruation following the relief of pressure, whether from a sellar decompression or from extirpation of the adenoma, would be strong evidence in support of such a view.* Hence particular importance

*At the present day, the old-time transphenoidal operations such as that mentioned in Case V, even in patients with a widely expanded sella easily approached from below, have been superseded by a more radical direct attack on the tumour by a transfrontal osteoplastic procedure.

is attached to the group of cases in which menstruation has returned after operation.

(a) *In Chromophilic Adenomas.* Of the 27 acromegalic women under fifty years of age with amenorrhoea who were operated upon (almost invariably for the relief of chiasmal symptoms), 5 had a post-operative return of normal menstruation.* In two patients the first period made its appearance three days after the operation, there having been in one instance an antecedent amenorrhoea of three months and in the other of nine months, this latter patient having subsequently become pregnant, but miscarried after six months. A third patient, after twelve months of amenorrhoea, resumed her normal menstruation two months after the operation, became pregnant five months later and had a normal full-term parturition. In a fourth, after six months of amenorrhoea, and in the fifth after six years of amenorrhoea, the menses became re-established, though after a somewhat longer interval, making the direct influence of the operation less probable.

(b) *In Chromophobe Adenomas.* Of the 70 women with adenomas of chromophobe type, all with accompanying amenorrhoea, ten had a subsequent return of regular menstrual periods. Three of these patients had a sella within normal limits and the other seven sellas that were moderately enlarged. Since in chromophobe adenomas amenorrhoea is so much more definitely a fixed symptom than it is with the adenomas associated with acromegaly, these cases may deserve special reference.

A successful operation for the removal of a suprasellar adenoma with a small sella would be expected to restore normal conditions, the subjacent gland not having been necessarily compressed. The following is an example of this.

CASE VI. (Surgical No. 27759.) *Amenorrhoea with chiasmal symptoms of 8 months' duration. Partial removal of suprasellar adenoma with temporary return of normal vision but no menstruation. After a second more radical operation, menstruation returned for 6 months, when it ceased again in association with recurring visual failure. A third still more radical operation followed by second return of menstruation still present after two years.*

History. Mrs. G., aged 43 years, was admitted December 7, 1926, complaining of failing vision. She had been married for nineteen years and had five children. Menstruation commenced when she was sixteen and apart from the pregnancies had been regular until the onset of the present illness. The periods suddenly ceased eight months before admission. Pregnancy was at first suspected, and then the menopause. Four months before admission she discovered that the vision in the left eye was becoming defective. There had been no headache or other symptoms.

Examination. This was entirely negative except for a bitemporal hemianopsia with central scotoma on the left with a questionable early optic atrophy. The sella was small (Fig. 8). The diagnosis was a suprasellar lesion, probably meningioma, and on December 13, 1926, a transfrontal exploration disclosed a suprasellar chromophobe adenoma which was incompletely removed. Vision promptly returned to normal.

*The same sequence of events has been observed in one or two acromegalic women who without operation had been subjected to vigorous X-ray treatment, but such an effect has never been observed after radiotherapy for chromophobe adenomas, these latter lesions being notoriously more resistant to radiation than the adenomas of acromegaly.

The patient continued to be symptom-free for three months when there was a return of her blurred vision in the temporal fields. This progressed rapidly and she was readmitted on May 2, 1927. The fields at this time showed as before a complete bitemporal hemianopsia with a large central scotoma on the left. There had been no return of menstruation.

At the second operation on May 7, 1927, a more radical procedure was carried out by means of suction, again with a rapid postoperative return of visual acuity and fields to normal. Menstruation returned the next month (June) and continued regularly until November, 1927, when it ceased and the vision once more became obscured.

She was admitted for a third time on January 11, 1928, with an incomplete bitemporal hemianopsia. At the third operation on January 17, 1928, the recurrent adenoma was removed within its capsule from the pocket beneath the chiasm. She made an excellent recovery and was soon discharged with sight again restored and essentially normal fields. Menstruation soon reappeared and had continued with normal periodicity for two years when on February 19, 1930, she was last heard from.

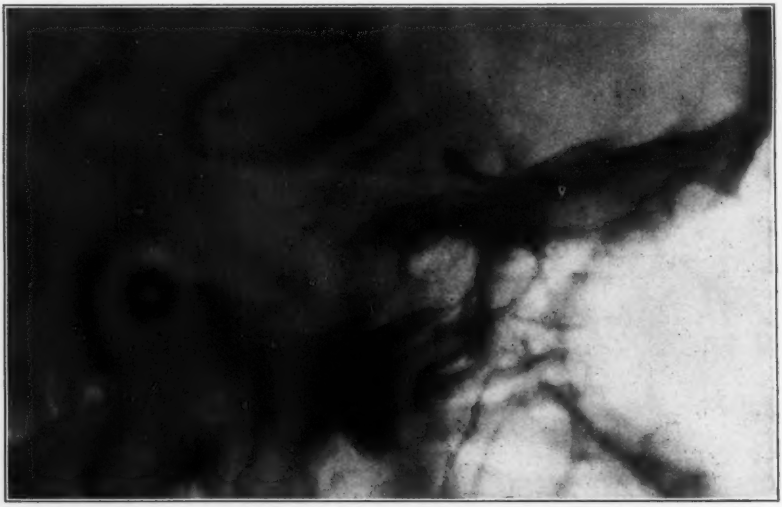

Fig. 8. (Case VI.) A small atrophic sella of a patient with a suprasellar adenoma.

This case differs from the usual one in that the pituitary fossa was small and the adenoma lay above it. There are, however, two patients in the series with the fossa well expanded by an intrasellar adenoma in whom not only was there a postoperative re-establishment of the menstrual cycle but pregnancy supervened with the birth of a normal child.

CASE VII. (Surgical No. 3657.) *Amenorrhoea of three years' duration followed by increase of weight and chiasmal symptoms. Transphenoidal operation. Resumption of menstruation five months later. A subsequent pregnancy.*

History. Mrs. E. R., aged 27, was admitted October 6, 1915, with the history of having married in 1907 at the age of 19 and of having given birth to a healthy child a year later. She had no further pregnancies, experienced a loss of libido, and finally in 1912 became completely amenorrhoeic. She meanwhile gained thirty pounds in weight, began to have dull headaches and finally was conscious of impairment of visual acuity.

Examination. This showed a young woman somewhat overweight with primary optic atrophy, a bitemporal hemianopsia, a slight enlargement of the sella (Fig. 9) and a basal metabolic rate of —22 per cent.

On October 9, 1915, a transphenoidal operation was made, the bulging thin floor of the sella and a considerable amount of adenomatous tissue being removed. There was prompt improvement in vision with early re-establishment of normal field peripheries. She was discharged October 19th, had her first menstrual period five months later on March 6th, with seventeen subsequent normal periods, when she became pregnant. Nine months later a healthy child was born which was nursed for eight months. The catemenia subsequently became re-established, but the periods were increasingly scant and finally ceased.

Three years later, vision had again become seriously impaired and she was operated upon by a surgeon in another city, this time by a transfrontal procedure; the tumour was exposed from above and radically excavated. She subsequently again began to menstruate, though irregularly, and was continuing to do so when she last reported in February, 1931.

Fig. 9. (Case VII.) A slightly enlarged sella with posterior clinoids pushed backwards by an expanding intrasellar adenoma (nat. size).

The story of the other patient with restoration of catemenia and subsequent pregnancy follows:

CASE VIII. (Surgical No. 4618.) *Amenorrhoea of 19 months' duration following childbirth and associated with evidence of pituitary tumour. Transphenoidal operation with resumption of menstruation and subsequent pregnancy followed again by amenorrhoea.*

History. Mrs. Mary M., aged 36, was admitted April 23, 1916. She had been married twelve years and had given birth to six children, the youngest nineteen months of age. Whereas she had had a superabundance of milk after her earlier pregnancies, she had been obliged to wean the last child after two months owing to insufficient lactation. Since the birth of this last child menstruation had never been resumed and she had been subject to severe headaches associated with diplopia. Vision had been failing for four months.

Examination. This showed a woman approaching middle age who was somewhat adipose. There was definite pallor of the optic nerves, bitemporal field defects and a medium enlargement of the sella which showed evidence of absorption of its floor. The basal metabolic rate was —4 per cent.

On May 5, 1916, a transphenoidal operation was performed. The sphenoidal cells were found to be filled with adenomatous material, large masses of which were removed. There was immediate postoperative improvement in vision with restoration of normal fields. She was discharged on May 19th greatly improved.

Normal menstruation was soon re-established and a year later she became pregnant, a healthy child being born in July of 1918. She was again obliged to wean this child owing to insufficiency of milk, and after two scanty menstrual periods amenorrhoea again set in, together with evident return of neighborhood symptoms associated with polyuria, polydipsia, failing vision and so on.

She re-entered the hospital on December 30, 1919, at which time the former symptoms were found greatly exaggerated, with complete destruction of the dorsum sellae, blindness in the left eye and a temporal hemianopsia on the right, with reduction of vision to 10/200 and a basal metabolic rate of —16 per cent. An attempted transfrontal operation was undertaken at this time, but owing to marked intracranial tension, presumably due to an intracranial extension of the adenoma, the procedure was abandoned short of bringing the chiasmal region into view. She was discharged unimproved and died September 1, 1921, with an advance of her intracranial symptoms.

In stressing these ten examples of chromophobe adenoma in which resumption of the menstrual cycle had followed operation, it is only fair to say that in five patients in the series there was a spontaneous reappearance of menstruation after a varying period of amenorrhoea, unrelated to operative intervention. In all of these cases, however, the periods were scanty and irregular, often with lapses of several months. There have been no examples in the series of patients with a widely ballooned sella in whom there was either a spontaneous or a postoperative resumption of menstruation.

(2) SEXUAL DYSFUNCTION IN THE MALE

In males victimized by pituitary adenomas there is no objective phenomenon like menstruation to serve as an index of the activity of the reproductive organs and we must have recourse to other less dependable criteria such as libido, testicular atrophy and impotence of which some mention is made in the history of nearly every male patient. There is, in general, a corresponding relationship between the size of the sella and the disturbance of libido just as there is with menstruation. The disturbance, however, develops somewhat later as shown by the large number with libido unaffected even in the presence of a large sella. What is significant, however, is that in none of those with a small sella is there complete loss of libido. The other evidences of sexual inactivity such as testicular atrophy and impotence are ordinarily present only in the later stages when the tumour has reached a large size.

Though these matters had been put in tabular form for both chromophobe and chromophilic adenomas in the male, in correspondence with the effects shown in Tables I and II for menstruation in the female, the data are necessarily less exact than in women and hardly deserve more than this brief mention. As in experimental work on animals, the clinical study of the sex hormone is more profitable in the female than the male. Nevertheless there can be no doubt that the effects of its loss are the same in both sexes.

SUMMARY

1. There are three types of cells in the anterior hypophysis—acidophilic, basophilic and neutrophilic or chromophobe, each of which is capable of the formation of an adenoma. The acidophilic adenomas are accompanied by acromegalic overgrowth long looked upon as a hyperpituitary state. The chromophobe adenomas, the most common type, are space-occupying lesions, composed of cells that secrete no known hormones and which provoke symptoms supposedly the reverse of acromegaly and consequently regarded as hypopituitary states. Basophilic adenomas have been described but they are minute structures whereas both of the others may attain a large size.

2. It has long been known that sexual dysfunction strikingly shown as amenorrhoea in the female is a common sequence of the more common adenomas whether acidophilic or chromophobe. As these were supposed to produce counterpoised states, their similar effect on the activities of sex was difficult to understand.

3. It has been experimentally demonstrated in recent years that the anterior lobe elaborates two hormones—one of them controlling growth, the other the functions of sex, the former being a product of the acidophilic cells, the latter of the basophilic cells. Destruction of these two elements by injury or disease leads to cessation of growth and to the interruption of the sex cycle of which ovulation in the female is the essential factor.

4. An analysis of the disorders of sex in 367 cases of hypophysial adenomas makes it apparent that the sexual dysfunction occurs only when the sella turcica has become considerably expanded and that there is no difference in this respect between the two common types of adenoma. The sexual dysfunction therefore may be assumed to be due solely to the compression of the basophil cells by the space-occupying lesion. Favourable to this mechanical view of the process is the fact that the normal menstrual cycle may be resumed and pregnancy occur after favourable operations with radical extirpation of the adenoma.

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ANTERIOR PITUITARY THERAPY IN SPONTANEOUS OVARIAN DYSFUNCTION

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That the anterior lobe of the hypophysis cerebri exercises some regulatory control over the gonads has long been suspected from clinical observations (Cushing, 1912) and Fröhlich (1901). Various sexual aberrations such an infantilism, dysmenorrhea, and amenorrhea have been ascribed to some hypophysial disorder. It remained, however, for Smith (1926) to demonstrate, by experimental means, the probable direction of this control. He was able to show that all sexual development and function is inhibited in hypophysectomized animals, and that replacement therapy may correct the resultant conditions. A further step was made in the similar, but independent researches of Smith and Engle (1927), and Zondek and Aschheim (1927). These workers demonstrated that immature rats and mice may be induced to a precocious maturity by the daily implantation of fresh pituitary glands.

The subsequent use of chemical extracts of the anterior lobe has confirmed and extended these original findings. Evans (1924), in a pioneer research, reported that the injection of saline and sodium hydroxide extracts of bovine pituitaries caused a cessation of the oestrous cycle in female rats. These observations have been confirmed and it now appears that two hormones which exercise a regulatory control over the ovary are produced in the anterior pituitary. The first of these is instrumental in bringing about follicular maturation, the second causing luteinization of follicles. This idea is disputed by some authors who consider that the variations of hormonal quantity and of gonadal susceptibility may explain the results which indicate the existence of more than one hormone.

The injection of fresh pituitary substance into adult rats and mice (Smith and Engle, 1927) causes super-ovulation. It appears that the number of follicles which are matured at any oestrus may be roughly proportional to the quantity of maturity hormone available. Friedman (1929) reports the induction of ovulation in the rabbit, a non-spontaneously ovulating form, following the injection of anterior lobe material.

Zondek and Aschheim (1927) have shown that senile mice may be induced into oestrus by the application of the pituitary treatment.

Marrian and Parkes (1929) have reported that rats suffering from inanition or Vitamin B deficiency, and the resultant condition of anoestrus, may be induced to normal ovarian activity following the administration of anterior lobe material.

These various results have adequately demonstrated that the seat of gonadal control lies in the anterior pituitary, and they suggest that most aberrations of gonadal function may have their origin in a derangement of the normal pituitary-gonadal relationship.

Technical Procedure. During the course of a separate investigation wherein the author had occasion to follow the oestrous cycles of several hundred rats over a considerable period of time, eight animals were found which, for at least five weeks, exhibited no oestrous changes whatever. These animals were apparently in the best of health and quite normal in every respect except for their reproductive cycles. Age, inanition, and Vitamin B deficiency could be ruled out as causative factors, since the history of each animal was known. The possibility suggested itself that some factor in the normal pituitary-gonadal relationship was inactive in these animals.

After a period of anoestrus lasting from five to seven weeks one ovary and a portion of the uterus were removed in each instance. All material was fixed in Bouin's and prepared for histological study. Coronal sections were cut at eight micra and were stained with haematoxylin-eosin. The animals were allowed two weeks for recovery and a close check was maintained on their vaginal smears. No oestrous changes occurred in any case. Seven of the animals were injected intramuscularly with one fresh anterior lobe (rat) each day. A modification of the technique described by Smith and Engle (1927) was employed for these implantations. The eighth animal was given subcutaneous injections of an extract prepared from sheep pituitary.* The amount employed was 0.5 cc. daily, since from data collected on immature rats this dosage seemed to approximate one rat gland in its effect on the ovary. The subsequent treatment varied in individual cases and will be described in connection with the results.

Experimental. In every instance oestrus occurred on the third or fourth day following the instigation of treatment. The smear of flaky, cornified cells was typical in every respect of a normal oestrus and was preceded by the usual pro-oestrous picture.

Two of the animals (CR_2L_2 and BL_2) were sacrificed on the day of oestrus. The remaining ovary and uterine horn presented the typical condition of oestrus. Large follicles were present in the ovary and the uterus was distended with liquor folliculi.

In two cases the animals (ER_1L_2 and CR_4L—) were sacrificed on the day following oestrus and a recovery of the uteri and ovaries was made at that time. The ovaries showed evidence of freshly ruptured follicles undergoing the customary transformation into corpora lutea. Histological study of these ovaries confirmed this and also revealed a number of very large, unruptured follicles. These latter were doubtless cystic in nature.

*This extract was kindly supplied by Dr. Oliver Kamm, of Parke, Davis & Company.

Smith and Engle (1927) have called attention to the tendency of adult rat ovaries to become cystic following anterior lobe implantation.

As a control measure, two females (BL_4 and BL—) were treated with proportional amounts of minced muscle tissue in precisely the same way as in the pituitary treatment. No change in the vaginal smear could be demonstrated over a ten day period. These same animals were allowed a rest of ten days and were then given daily injections of anterior lobe material. Both responded on the third day, and when at the height of oestrus, were placed with fertile males. Coitus occurred in each instance and was followed by a normal pregnancy. Parturition took place on the twenty-first day, each mother giving birth to five young, whose subsequent growth was quite normal.

The remaining two rats (BR_2L_2 and DR_1L_3) were given the regular anterior lobe treatment, and after the appearance of oestrus were allowed to live in order to ascertain if the normal rhythm would be maintained following the discontinuance of treatment. Over a two weeks' period no further cyclical events were observed. Their pituitaries were then removed on successive days and implanted into a twenty-four day old female. Her vagina opened on the third day and autopsy findings demonstrated the expected picture of oestrus in the uterus and ovaries.

DISCUSSION

The rapid response of these non-cyclic females to anterior pituitary therapy seems to justify the initial supposition that some factor in their pituitary-gonadal relationship was inactive. We are reasonably certain at the present time, that, of the entire endocrine series the anterior hypophysis is the only gland which is fundamentally concerned with the normal functioning of the gonads. In all probability other glands, notably the thyroid, have their rôles in the maintenance of gonadal function, and disturbances in them may well be reflected in the gonads. However, all recent work has served to relegate them to a position of minor importance and has elevated the hypophysis to the major rôle.

Recognizing that the etiological factor responsible for the ovarian dysfunction of the animals studied in this work was probably some unit in the pituitary-gonadal relationship, it is of interest to consider the points which are most likely to prove vulnerable in the chain of events extending from the production of the hormone in the anterior lobe to its utilization in the ovary. First, the pituitary may not be producing the hormone essential for follicular maturation; second, production may be occurring normally, but for some reason the hormone is not released into the blood stream; third, the renal threshold for the hormone may be lowered to such a degree that it is not available to the ovary in sufficient quantity to permit normal ovarian function; fourth, the ovary may not be in a condition to respond to the stimulus afforded by the hormone, although the latter be present in sufficient amounts.

The first of these points is answered by the experiment in which the pituitaries of animals BR_2L_2 and DR_1L_3 were implanted into an immature rat and subsequently induced maturity. This indicates that the hormone was being produced although it was not being utilized by the hosts, and recalls the observations of Smith and Engle (1927) on the use of pituitaries from immature and senile rats in the induction of precocious puberty. The fourth point is adequately answered by any one of the eight cases. Corey (1930) has shown that the implantation of anterior lobe substance into foetuses "in utero" has no pronounced effect upon their gonads. This is explained upon the basis of the inability of the gonads to respond fully to hormonal stimulus during foetal life. Smith and Engle (1927), in their studies on post-natal animals have found that the duration of treatment necessary for the induction of puberty is inversely proportional to the age of the animal. The invariable and identical response of the females used in the present study indicates that the gonads were in a susceptible condition, and that their faulty behavior had a common basis other than a lack of responsiveness to the hypophysial stimulus. The third point, that of a possible decrease in the renal threshold for the maturity hormone, is less readily answered. Our present knowledge concerning the renal threshold levels of the various hormones is extremely scanty. It is possible that this decrease may occur in some cases of gonadal dysfunction, but it is reasonable to suppose that if this explanation is applicable to the animals studied in this work, then the supplied hormone should likewise have been eliminated before any change in the ovaries was effected. The remaining point of weakness in the hypophysial-gonadal relationship—the non-release of the hormone from the gland—seems to be the most logical explanation for the failure of these animals to exhibit a normal reproductive cycle. The experiments in which the pituitaries of animals CR_2L_2 and DR_1L_3 were employed to induce precocious puberty serves to indicate that the maturity hormone was being produced in normal quantities. This observation recalls the work of Engle (1929) on the use of anterior lobes from castrate rats, and the studies of Smith and Engle (1927) on the employment of glands from immature and senile animals. The anterior pituitaries of any of the aforementioned types of animals, while incapable of exerting their normal effect on the gonads of their owners, are active when implanted into a new host. This fact is not inharmonious with the work of others. Swingle (1923) has reported that the thyroid of neotenous amphibia will liberate its secretion when transplanted, and Charipper and Corey (1930) have shown that the pituitary of these forms behaves similarly. Uhlenhuth (1919) has postulated an "excretor substance" in connection with a "releasing mechanism" which is supposed to be operative in the thyroids of amphibia.

That the pituitaries of these sexually aberrant females were liberating some gonadal-stimulating hormone is quite apparent from the histological

picture of their ovaries prior to treatment. There is no evidence of the widespread follicular atresia seen in hypophysectomized animals (Smith, 1926). Hence we are obliged to conclude that here, as in the case of young females, the pituitaries were releasing some of their hormonal content, but less than they were potentially able to liberate. It must be admitted that the degree of ovarian maintenance exhibited by these animals might also be considered as evidence in favor of a decreased renal threshold level for the maturity hormone.

The successful pregnancies of BL_4 and BL— are interesting inasmuch as they demonstrate that the normal sequence of events attendant upon conception and pregnancy was carried out by the reproductive apparatuses of these treated females.

The failure of animals BR_2L_2 and DR_1L_3 to maintain an oestrous rhythm following the cessation of treatment is not surprising. Immature females stimulated to precocious puberty do not continue ovulating at periodic intervals unless the time of induced maturity is near that normally attained. Instead, they lapse into a condition of sexual inactivity until the normal age of puberty is reached. The same is true of females induced to sexual activity after the menopause. The pars anterior treatment, therefore, does not establish permanently the adult relationship between pituitary and ovary, but merely furnishes a transitory stimulus to the ovary. It would seem that a complex of factors, which we do not understand at the present time, is operative in the establishment and maintenance of the hypophysial-gonadal relations. Just what effect a more chronic treatment of animals BR_2L_2 and R_1L_3 would have had on the permanent re-establishment of normal relations is a point of speculative interest.

In view of the present results in the employment of anterior lobe therapy in cases of spontaneous ovarian dysfunction, it seems likely that the clinical application of a similar treatment would correct many cases of human sterility. However, such therapeutic measures would probably be effective only in instances in which sterility is the result of a defective pituitary-gonadal relationship. Just what percentage of sterility in man is of this type is unknown at the present time, but in all probability many of the cases which have no apparent etiological background may be classed as such. Recently, considerable clinical use has been made of the follicular hormone in various types of gonadal dysfunction. Although such treatment may induce some effect on the uterus and vagina, the follicular hormone has no stimulating effect on the ovary. Indeed, a result quite the converse occurs. Allen and Doisy (1924) conclude that ovulation is repressed in oestrin-injected mice, and Mahnert and Siegmund (1927) report the same condition in women. Most of the recent work tends to render oestrin therapy basically unsound in cases of sterility. Smith and Engle (1929) report that the pituitaries from female guinea-pigs in oestrus

are less efficacious in inducing premature puberty than are glands from animals in dioestrus. Mayer, Leonard, Hisaw and Martin (1930) injected rats with oestrin for 40 days and found that their pituitaries were much less efficient than those of untreated animals. Moore and Price (1930) consider that oestrin diminishes the hypophysial output and so serves as a dynamic factor in the pituitary-gonadal relationship. Hartman, Firor and Geiling (1930) recently introduced an opposite view, holding that oestrin stimulates the hypophysis to activity. This latter work is interesting in connection with the present report. Hartman and his collaborators, working on the Macaque monkey, were able to induce menstrual bleeding by the injection of an anterior lobe extract. They believe that the anterior hypophysis secretes a hormone concerned only with the production of some change in the uterine endometrium which is instrumental in permitting the extravasation of blood. Just what effect this new aspect is to have on our present conception of the dynamics of the menstrual cycle remains to be seen. Certainly, it in no way obviates the suggestion that the anterior lobe may be employed as a corrective agent in some types of human sterility.

SUMMARY

1. Eight adult female rats, which for at least five weeks had shown no oestrous changes in their vaginal smears, were given daily implants of anterior lobe, or daily injections of an extract prepared from anterior lobe material.

2. Oestrus occurred, in each instance, on the second or third day subsequent to the instigation of treatment.

3. The ovaries and uteri prior to treatment presented a picture approximating that of dioestrus, while the remaining ovaries and uteri removed subsequent to the occurrence of the induced oestrus were either of an oestrous or meta-oestrous character.

4. When copulation was permitted at the time of induced oestrus, successful pregnancies resulted.

5. The pituitaries of these females were capable of promoting precocious maturity in a young rat when introduced intramuscularly.

6. No further oestrous changes could be demonstrated beyond the initial induced oestrus.

7. It is concluded that the etiology of the aberrant ovarian behavior observed in these animals probably was some derangement of the normal hypophysial-gonadal relationship—possibly the non-release of the gonadal stimulating hormone.

8. Attention is called to the possible therapeutic value of anterior lobe treatment in some types of human sterility.

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THE EFFECT OF QUININE UPON THE THYROID GLAND

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Forchheimer was the first (circa 1885) to recommend on empiric grounds the use of quinine in thyrotoxic states. On the basis of his wide clinical experience he claimed that "the good effects of this treatment usually follow in the same sequence: first, the tachycardia improves, the pulse frequently coming down from 130-140 beats to 80 or 90 beats per minute in forty-eight hours; secondly, the thyroid gland diminishes in size, by measurement; thirdly, the tremor and exophthalmos disappear" (1). There have been a number of more or less enthusiastic reports on the use of various salts of quinine, chiefly the hydrobromide, in thyrotoxicosis (2). Clendening, in his text on "Modern Methods of Treatment" (3) states that "in the treatment of intoxication from the thyroid gland, quinine is the drug that I use as a routine most frequently." Although the drug has never come into general use, it is still routinely employed in some European clinics, and faith in its efficacy in hyperthyroidism persists in some quarters in this country. Bram, in particular, claims much for it: "Quinine is the drug 'par excellence' in the treatment of exophthalmic goiter" (1). In a clinical study of five hundred patients with Graves' syndrome, Bram (4) reported a material amelioration of symptoms in over 60 per cent of those on quinine therapy: "Within two or three weeks, an increase in weight occurred in many patients, a lessening of the excitability and tremor, reduction in the thyroid swelling and exophthalmos, marked lowering of the heart rate and a considerable reduction in the basal metabolic rate." In 95.6 per cent of the same series of patients, Bram observed a relative immunity to cinchonism, and on the basis of this remarkably constant increased tolerance to the drug, proposed that a "quinine diagnostic test" be used in all suspected cases of exophthalmic goiter. He concluded that "in the form of the hydrobromide, or the sulphate, quinine is a valuable constituent of the therapeutic armamentarium of the internist who treats patients with exophthalmic goiter." In other publications Bram has emphasized his experience in the successful medical treatment of Graves' syndrome without resorting to operation.

In confirmation of Bram's observation, Pfahler (5) noted that thyrotoxic cases could take large doses of quinine with impunity. Sainton and Schulman (6), on the other hand, found this drug worthless as a diagnostic aid in similar patients. The most important refutation of Bram's enthusiastic claims is the report of Means and Aub (7), who found that

quinine hydrobromide administered from one to three weeks was of no value in reducing the basal metabolism in exophthalmic goiter.

The advent of iodine therapy in toxic goiters has not entirely closed the question of the validity of the use of quinine. Although the striking beneficial effect of iodine in hyperthyroidism is now well known, many clinicians are agreed that an exacerbation of symptoms usually occurs during long continued iodine administration without operative intervention. Starr (8), after a careful clinical study, concluded that "the course of hyperthyroidism under iodine medication is characterized by remission and recurrence during the administration of iodine and by a reaction which may be extreme, after iodine is discontinued; hence, the prolonged treatment of patients who have hyperthyroidism with iodine in dosage sufficient to produce these effects is without final benefit." The advocates of quinine therapy in toxic goiter have stressed this point of superiority over the universally popular iodine preparations—i.e., that quinine may be used continuously with benefit for many months, and without fear of stimulation of thyroid activity.

The theoretical reasons which have been adduced to explain the alleged beneficial action of quinine in thyrotoxic states are greatly disputed. They are concerned chiefly with the evidence quoted in most standard texts on pharmacology (9, 10) that quinine lowers the nitrogenous tissue waste of the body, lessens the rise of temperature from muscular exertion (10), reduces the metabolism (for instance, the hippuric acid synthesis) in perfused organs, lessens the oxidation in excised muscles (11) —in general obtunds the heightened metabolism which characterizes thyrotoxicosis. Hardikar (12), however, made a critical review of the whole subject of the action of quinine on protein metabolism, respiratory exchange and heat function, pointed out fundamentally unsound methods used by previous investigators, and concluded from his own experiments that even large doses of quinine fail to show any alteration in the protein metabolism either in man or animals.

Mills (13) studied the effect on the thyroid of quinine bisulphate injected intramuscularly in varying doses daily for one week in six young growing rabbits. Using changes in the histological appearance of the secreting cells and the colloid of the gland as criteria of the functional activity of the thyroid at the time the specimens were taken, Mills concluded that quinine appeared to depress the activity of this organ. The mechanism of this action was thought to be a lessened protein metabolism leading to a diminished need for thyroid secretion in the body and allowing its storage as colloid in the gland vesicles. The histological picture of a "resting type" of gland which Mills described, consisted of an increased amount of follicular colloid, a decrease in the height of the epithelial cells, and a denser staining of both cells and colloid.

Sugata (14) confirmed the observations of Mills on the influence of

quinine on thyroid morphology in rabbits and dogs. The same investigator noted that quinine caused an increase in the iodine content and concentration in the thyroid gland in his experimental dogs.

Considering the persistent use of quinine by many of the older clinicians in the treatment of thyrotoxicosis, the present claims of Bram, and the conflicting clinical and laboratory evidence, it was believed that the subject deserved further investigation. It was the purpose of our experiments to study the histological effect of quinine, not only on the thyroids of normal animals, but also on those glands in which a compensatory hyperplasia had been produced by the previous removal of one and one-half lobes. Marine (15) has shown that this simple expedient provides a useful experimental approach to the histologically active thyroid gland. The apparently opposite influence of potassium iodide upon the thyroid gland of the rabbit as noted by Marine and Lenhardt (16) and upon the thyroid gland of the guinea pig as noted by Loeb and his co-workers (17), made it advisable to use both animals in our observations. Quinine therapy was also given a brief clinical trial in five carefully controlled cases of hyperthyroidism on the wards of Barnes Hospital.

Material and Methods.

After a week of control laboratory study, healthy rabbits weighing between 1600 and 3500 grams, and healthy guinea pigs weighing between 350 and 650 grams, were chosen. The animals were divided so as to utilize a proportionate number of light and heavy animals for each experiment. Males were used almost exclusively.

A solution of quinine HCl was used at first, but it was soon replaced with quinine HBr because of the greater ease in mixing, the clearer solution obtained and the increased resistance to deterioration. The amount of bromide was too small to produce any pharmacological action (18).

The daily dosage of quinine was calculated according to weight. Approximately 0.06 gram per kilo was chosen as the average dose. This represents about double the amount usually prescribed in clinical thyrotoxicosis in man.

In early experiments guinea pigs were given the quinine intraperitoneally, but this method produced a chemical peritonitis and was abandoned. The histological picture in the thyroids of these guinea pigs resembled so closely the picture in the thyroids of the animals who received quinine orally that we have included them in our results. The rabbits were all given the quinine by stomach tube. The guinea pigs were held firmly and the solution dropped on the backs of their tongues. The animals were held until all the fluid was swallowed. A fifty per cent excess above the required dose was administered to allow for loss.

For the study of the effect of quinine upon compensatory hypertrophy, one and one-half thyroid lobes were removed and, after two days were allowed for post operative recovery, the quinine administration was

started. All the animals received their required dose each morning before they were given food. The animals were killed by chloroform inhalation and the autopsies were performed immediately. Numerous sections were made of each specimen; several were cut serially.

In the microscopic examination certain features were studied; and these form the column headings for the ensuing tables. The size of the acini, the height of the epithelium, and the consistency of the colloid are the items to be emphasized. The presence of lymphocytes and phagocytes were investigated, but too few were found in the glands to deserve special mention. Histological activity of the thyroid gland is marked by a tall epithelium and a soft colloid; the reverse picture, low epithelium and hard colloid, connotes inactivity or the so-called resting state (13).

The experiments may be divided into four groups:

I. The effect of quinine upon the thyroid glands of normal rabbits.

II. The effect of quinine upon the compensatory hypertrophy of the thyroid of rabbits.

III. The effect of quinine upon the thyroid of normal guinea pigs.

IV. The effect of quinine upon compensatory hypertrophy of the thyroid glands of guinea pigs.

TABLE I

THE THYROID OF NORMAL RABBITS

No.	Experiment	Weight	Size of Acini	Epithelium	Colloid
264	Normal control		Medium	Cuboidal	Some vacuoles
265	Normal control		Medium	Cuboidal	Many vacuoles
268	Normal control	2300 gm.	Medium to large	Cuboidal	Hard, some vacuoles
395	Normal control	3600 gm.	Medium	High cuboidal	Many vacuoles
397	Normal control	2250 gm.	Medium	Cuboidal	Hard, few vacuoles
398	Normal control		Medium	Cuboidal	Hard, many vacuoles
399	Normal control		Medium to large	Cuboidal	Hard, some vacuoles
400	Normal control		Medium	Cuboidal	Hard, some vacuoles
406	Normal control		Small to large	Cuboidal	Hard, much softening
407	Normal control		Medium	Columnar	Much softening
414	Normal control		Medium	High cuboidal	Much softening
415	Normal control	1900 gm.	Medium	High cuboidal	Much softening
416	Normal control		Medium	High cuboidal	Much softening
417	Normal control	1725 gm.	Medium	Cuboidal	Many vacuoles
418	Normal control		Small	Cuboidal	Some vacuoles
419	Normal control	1575 gm.	Medium	Cuboidal	Some vacuoles
421	Normal control	1500 gm.	Small to medium	Cuboidal	Much softening

Since we had had no opportunity to examine large numbers of rabbit thyroid glands in this laboratory, we availed ourselves of as many thyroids as was possible. The microscopic picture of 17 glands is outlined in

Table I. The thyroid gland of the average rabbit exhibits medium-sized acini, with moderately high cuboidal epithelium and colloid which, although generally hard, displays a fair amount of vacuolization and softening.

TABLE II

THE THYROID OF QUININE TREATED RABBITS

No.	Experiment and Daily Dose	Weight Change	Size of Acini	Epithelium	Colloid
251	.13 Quinine HCl for 17 days	+40%	Medium	Cuboidal	Hard, some vacuoles
254	.16 Quinine HCl for 33 days	+16%	Medium +	Cuboidal +	Many vacuoles
256	.12 Quinine HCl for 33 days	+41%	Medium +	Cuboidal +	Many vacuoles
258	.15 Quinine HCl for 33 days	+14%	Medium +	Cuboidal +	Many vacuoles
259	.14 Quinine HCl for 30 days	+ 6%	Medium	Cuboidal + +	Many vacuoles
396	.25 Quinine HCl for 30 days	+ 2%	Large	Cuboidal	Hard, few vacuoles
422	.10 Quinine HBr for 30 days	No change	Medium +	Columnar	Softening
423	.18 Quinine HBr for 30 days	No change	Large, many small	Columnar	Softening
438	.28 Quinine HBr for 30 days	+ 7%	Large and small	Cuboidal + +	Many vacuoles
968	.22 Quinine HBr for 30 days	+ 8%	Medium to small	Cuboidal	Few vacuoles

Table II summarizes the effect of quinine upon normal rabbits. It will be seen that there is little difference between the histological picture of these thyroids and the thyroids of the control rabbits. The average size of the acinus, height of the epithelium and character of the colloid is approximately that of the thyroids shown in Table I. Both show variations, but these are not excessive either within the groups themselves, nor comparatively between the treated and untreated animals. It can be stated definitely that the method employed in these experiments demonstrates no change in the microscopic appearance and indicates neither stimulation nor depression of the thyroid gland.

TABLE III

COMPENSATORY HYPERTROPHY IN NORMAL RABBITS

No.	Experiment	Weight Change	Size of Acini	Epithelium	Colloid
268A	Control, 30 days	+18%	Medium	High cuboidal	Softening
269A	Control, 30 days	+18%	Medium	Cuboidal	Hard, some vacuoles
274A	Control, 30 days	+26%	Medium	Columnar	Very soft
419A	Control, 30 days	No change	Medium	Columnar	Very soft
421A	Control, 30 days	No change	Medium	High cuboidal	Soft

The thyroids described in outline in Table III give a fairly clear picture of compensatory hypertrophy. There is no change in size of the acini; the epithelium, however, is taller and the colloid exhibits more softening than in the thyroid glands of normal rabbits in Table I. In

three of the rabbits, 268A, 419A and 421A, by referring to Tables I and III, one may compare the histological appearance of the portion of the thyroid gland originally removed with the microscopic picture of the remaining one-half lobe thirty days later. Distinct changes similar to those just mentioned were found in all specimens, especially in rabbits 268A and 419A.

TABLE IV

QUININE IN COMPENSATORY HYPERTROPHY IN RABBITS

No.	Experiment and Daily Dose	Weight Change	Size of Acini	Epithelium	Colloid
260A	.12 Quinine HBr for 30 days	+ 4%	Medium	Cuboidal	Hard, few vacuoles
261A	.12 Quinine HBr for 30 days	+10%	Medium	Cuboidal	Hard in general, soft in few spots.
263A	.15 Quinine HBr for 30 days	+ 9%	Medium	Cuboidal	Hard
397A	.18 HBr for 13 days	+ 7%	Medium —	Cuboidal	Few vacuoles
415A	.15 HBr for 20 days	+70%	Medium	Cuboidal	Many vacuoles
417A	.15 HBr for 20 days	+ 2%	Medium —	Cuboidal	Some vacuoles
395A	.26 HBr for 20 days	+ 7%	Large	High cuboidal	Many vacuoles

In Table IV one notes a fairly definite effect of quinine. Except in one instance, the epithelium is decidedly lower than it was in the untreated rabbits listed in Table III. The colloid is also distinctly harder in the thyroids of the animals which received the drug. The histological picture of the thyroid glands in this series resembles very closely the appearance of the normal control rabbit thyroids which are described in Table I. Thus the administration of quinine to partially thyroidectomized rabbits seems to suppress the usual compensatory hypertrophy to such a degree that the remaining portion of the gland is microscopically indistinguishable from the lobe and one-half lobe originally resected. (Cf. Rabbits 395, 397, 415, and 417 in Tables I and IV.)

TABLE V

THE THYROID GLANDS OF NORMAL GUINEA PIGS

No.	Experiment	Weight	Size of Acini	Epithelium	Colloid
310	Normal control	680 gm.	Medium, small and large	Cuboidal —	Hard, some softening
387	Normal control	355 gm.	Medium, small	Cuboidal	Hard, some vacuoles
388	Normal control	520 gm.	Medium, small	Cuboidal	Some softening
390	Normal control	385 gm.	Medium, small	Cuboidal —	Hard, some vacuoles
391	Normal control	360 gm.	Medium, small	Cuboidal	Many vacuoles

Table V enumerates the important features in the histological picture of the normal guinea pig thyroid gland. Although there are only five animals included in this series, so many thyroids have been studied in Dr. Loeb's laboratory by one of us (SHG), that we are confident these speci-

mens are entirely representative. The acini tend to be medium to medium small in size, the epithelium medium to low cuboidal in height, and the colloid hard with occasional vacuolization and retraction. A few lymphocytes are found in the interstitial tissue. The normal thyroid shows a fair amount of variation in different areas of the gland itself, as well as in the glands of separate animals. This has been emphasized by Loeb and was taken into consideration in this study.

TABLE VI

THE THYROID GLAND OF QUININE TREATED GUINEA PIGS

No.	Experiment and Daily Dose	Weight	Size of Acini	Epithelium	Colloid
132	9 days, Quin., HCl .03 Intraperitoneal	—11%	Medium	Cuboidal —	Hard
134	9 days, Quin., HCl .03 Intraperitoneal	—21%	Medium	Cuboidal	Hard, occasional vacuolization
135	9 days, Quin., HCl .03 Intraperitoneal	—28%	Medium	Cuboidal	Hard, few vacuoles
137	12 days, .03 Quin., HCl Intraperitoneal	— 7%	Medium	Cuboidal	Solid
138	11 days, .03 Quin., HCl, Intraperitoneal	No change	Medium, some large	Cuboidal	Hard, some vacuoles
139	6 days, .03 Quin., HCl, Intraperitoneal	—27%	Medium, some large	Cuboidal —	Hard
140	11 days, .03 Quin., HCl, Intraperitoneal	No change	Medium	Flat	Hard
408	30 days, .06 Quin., HCl by mouth	+ 3%	Medium	Cuboidal	Hard
409	30 days, .06 Quin., HCl by mouth	+12%	Medium	Cuboidal —	Hard
410	30 days, .06 Quin., HCl by mouth	+20%	Medium	Cuboidal	Hard, some vacuolization
411	30 days, .06 Quin., HCl by mouth	+22%	Medium, some large	Cuboidal	Hard
112	30 days, .06 Quin., HCl by mouth	—23%	Medium	Cuboidal +	Hard, some vacuoles
413	30 days, .06 Quin., HCl by mouth	+ 9%	Medium	Cuboidal —	Hard, some vacuoles
606	30 days, .06 Quin., HCl by mouth	+20%	Medium	Cuboidal	Hard

Of the fourteen animals in this experiment, the first seven received the quinine intraperitoneally. All of these animals were sacrificed when they appeared sick, except one (number 140), which was found dead. In this instance the post mortem examination was made about five hours after death. All of the seven guinea pigs which had received intraperitoneal injections of quinine hydrochloride showed a chemical peritonitis. It will be seen from studying Table VI, that the histological picture in this entire group, whether the animals received the quinine intraperitoneally or by mouth, is rather uniform and very similar to the microscopic picture of the untreated guinea pigs (Table V). Thus we may assume that quinine produces no change in the thyroid gland of the normal guinea pig.

TABLE VII

COMPENSATORY HYPERTROPHY IN UNTREATED GUINEA PIGS

No.	Experiment and Daily Dose	Change in Weight	Size of Acini	Epithelium	Colloid
143	18 days, C. H. control	+ 3%	Medium	Cuboidal ++	Softening
146	18 days, C. H. control	+15%	Medium	Cuboidal ++	Softening
147	20 days, C. H. control	—15%	Medium	Cuboidal +	Some softening
299	30 days, C. H. control	+22%	Medium +	Cuboidal	Much softening
308	30 days, C. H. control	+ 5%	Medium	Cuboidal	Some vacuoles
309	30 days, C. H. control	+16%	Medium, some large	Cuboidal	Some vacuoles
387	30 days, C. H. control	—10%	Medium	Cuboidal ++	Much softening
388	30 days, C. H. control	+18%	Medium	Cuboidal ++	Some softening

Although Table VII does not show as much compensatory hypertrophy as one may find in guinea pigs, the change toward a taller epithelium and a softer colloid is definite. This can be readily seen in animals 387 and 388, where the thyroid gland was examined before and after the removal of one and one-half lobes.

Five of the eleven animals listed in the above table were given the calculated dose of quinine by intraperitoneal injection and sacrificed upon the sixteenth day. Here also we can see by reference to Table VIII and

TABLE VIII

COMPENSATORY HYPERTROPHY IN QUININE TREATED GUINEA PIGS

No.	Experiment and Daily Dose	Change in Weight	Size of Acini	Epithelium	Colloid
144	16 days, Quin., HCl .03 Intraperitoneally daily	—14%	Medium +	Cuboidal	Much vacuolization
150	16 days, Quin., HCl .03 Intraperitoneally daily	—17%	Medium +	Cuboidal ++	Much softening
151	16 days, Quin., HCl .03 Intraperitoneally daily	— 9%	Medium +	Cuboidal ++	Softening
152	16 days, Quin., HCl .03 Intraperitoneally daily	— 9%	Medium +	Cuboidal +	Some softening
154	16 days, Quin., HCl .03 Intraperitoneally daily	— 8%	Medium —	Cuboidal ++	Some softening
306	30 days, Quin., HCl .06 daily, by mouth	— 7%	Medium	Cuboidal +	Many vacuoles
310	30 days, Quin., HCl .06 daily, by mouth	No change	Medium —	Cuboidal —	Hard, few vacuoles
321	30 days, Quin., HCl .06 daily, by mouth	+ 6%	Medium	Cuboidal	Hard, some softening
390	30 days, Quin., HCl .06 daily, by mouth	+ 3%	Medium —	Cuboidal —	Hard
391	30 days, Quin., HCl .06 daily, by mouth	— 8%	Medium	Cuboidal ++	Many vacuoles
392	30 days, Quin., HCl .06 daily, by mouth	—11%	Medium	Cuboidal +++	Softening

by comparison with the orally treated animals that there were no significant histological differences related to the method of administration of the drug. The size of the acini, the height of the epithelium and the consistency of the colloid in nine of these eleven animals vary little, if at all, from the picture noted in compensatory hypertrophy in Table VII, where the animals received no treatment. It would appear from this that quinine has little, if any, effect upon compensatory hypertrophy in the thyroid gland of the guinea pig.

DISCUSSION

From these experiments the conclusion seems justified that quinine appears to suppress compensatory hypertrophy of the thyroid gland in the rabbit. The drug has no definite effect on the normal thyroid gland of the rabbit or guinea pig. No constant influence was noted on compensatory hypertrophy of the thyroid gland of the guinea pig.

The effect of quinine on compensatory hypertrophy of the rabbit thyroid gland resembles closely the effect of iodine noted by Marine (16) in the same animal.

The discrepancies between our experimental results and those of Mills (13) may be explained by differences in the dosage of quinine used, the method of administration of the drug, and the longer period over which we had the opportunity of observing a larger series of experimental animals.

CLINICAL TRIAL OF QUININE

Five cases of previously untreated exophthalmic goiter were selected on the adult medical service at Barnes Hospital. The patients were given a preliminary period of observation with complete rest in bed and high caloric diet, during which time the basal metabolic rate was taken every third day. After a level was reached in which there were no further noteworthy changes in the basal metabolism, quinine sulphate was given by mouth in the average dosage of 2 grams (30 grains) daily (0.6 gm. t.i.d. p.c.). The drug, thus administered for from two to three weeks, did not cause in any instance a significant fall in the metabolic rate, nor any improvement in the clinical signs of hyperthyroidism. The increased tolerance to quinine which Bram (4) has emphasized was a constant finding in our short series of cases. In one individual, a young colored woman with a mildly toxic Graves' syndrome, 2 grams (30 grains) of quinine sulphate were taken daily without any symptoms of cinchonism before operation, whereas a capsule of 0.3 grams (5 grains) of the drug after thyroidectomy caused violent tinnitus and vertigo.

In four of the five patients, quinine had to be abandoned as the sole preoperative medicament because of undesirable side effect (such as loss of appetite which interfered with the essential high caloric diet) or be-

cause there was not sufficient clinical improvement to warrant the risk of thyroidectomy. Since these individuals were given routine preparation with Lugol's solution (19) after the discontinuance of quinine, no conclusions can be drawn as to the effect of the latter drug on the pathological appearance of the resected thyroid glands. In the one case operated on after only quinine sulphate preparation, the histological picture of the thyroid gland showed focal hypoplasia, and moderate increase of colloid such as is often noted in exophthalmic goiter patients who have received insufficient preoperative iodine.

SUMMARY

The authors have studied the effect on the thyroid gland of quinine hydrochloride and quinine hydrobromide administered to rabbits and to guinea pigs for several weeks in amounts proportionately double the human dosage. It was found that experimentally quinine caused regressive histological changes in compensatory hyperthrophy in the thyroid gland of the rabbit, but not of the guinea pig. Quinine in repeated, relatively large therapeutic doses had no effect upon the histological appearance of the thyroid gland of the normal rabbit or guinea pig.

Carefully controlled observations in five cases of exophthalmic goiter treated with quinine sulphate revealed no beneficial clinical effects.

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EUNUCHOIDISM ASSOCIATED WITH EMACIATION

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The number of metabolic observations carried out on human male castrates and eunuchoid individuals is necessarily small. Tandler and Gross (1) made a classic contribution on the subject in their monograph published in 1913. These authors gave careful descriptions of the physical characteristics of male castrates but made little note of any metabolic disturbances. Lipschutz (2) in 1924 made a survey of the literature but dealt more particularly with physical than metabolic observations. Rowe and Lawrence (3) have applied their very systematic method of physical and metabolic observations, as used in other endocrine conditions, to the study of a group of eleven males showing hypo-functional gonad disturbances. This group included adult castrates and younger individuals showing arrest of sex development. It is felt that the case to be described may be of interest especially since he showed evidence of faulty sex development with accompanying skeletal changes which must have begun in early youth.

CASE No. 10861. A white male, unmarried, 48 years of age, a cook by occupation, was admitted to the University Hospital in January, 1931, with bronchitis.

Physical Findings. On routine physical examination it was discovered that he presented certain definite eunuchoid characteristics. He had a thick growth of hair on his head which was much finer than one meets in the average adult male. The face had a wasted appearance and the skin of the cheeks showed very obvious wrinkling. The hair on the face was very sparse with a fair growth on the chin and above the corners of the mouth, while the middle of the upper lip, the skin underneath the chin, the cheeks and the upper part of the neck were practically hairless. There was a scanty growth of fine hair in the axillae. The skin of the trunk and extremities was soft, smooth, and free from hair. The pubic hair was fine, straight, and showed the female type of distribution with a straight upper margin. There was absence of hair around the anus. Examination of the genital organs showed bilateral atrophy of the testes. They were equal in size and no larger than a bean. The penis was under-developed, the prostate was atrophied and could not be palpated. The gluteal region and the area over the trochanters showed an increased laying down of fat. There was an increased amount of fat over the symphysis pubis, giving the appearance of the female mons veneris. The skeletal findings were striking. The pelvis was widened and the legs and arms were disproportionately long as compared with the trunk.

Personal and Family History. The patient was the last child of a family of twelve. His mother was 40 years old and his father 45 when he was born. He has four brothers and three sisters alive and well, all of whom are married and have children. One brother, he states, is as hairless as himself. He left school at the age of twelve when he was in grade IV. He does not think he was backward at school.

Signs of puberty developed late. He began to shave at eighteen and since then has only shaved every week or ten days. He has never had any body hair. He states that he had normal sexual vigour until fourteen years ago. Since then he has not experienced sexual desire nor erection. He associates this loss of libido with an injury sustained two years previously while in the army. He fell down a pit and injured himself in the scrotal area. There was no swelling or ecchymosis of the testes or scrotum following the accident and he did not have

to take to bed. He states, however, that his testes began to grow smaller and that he lost 40 pounds weight following the accident. His story may not be trustworthy as he is at present trying to establish a case for compensation.

He has had no previous illness except influenza in 1918. He has not had mumps.

DATA

The investigation of the patient was carried out along the lines suggested by Rowe and Lawrence (3). It is of interest, therefore, to compare the findings in this patient with the average of the findings in the eleven males showing hypogonadism described by the above authors.

Physical Measurements.

	Patient	Rowe & Lawrence Average
Height	176 cm.	166 cm.
Sitting Height	81 cm.	88 cm.
Sitting Height Index	0.460	0.530
Chest Circumference	84 cm.	87 cm.
Trunk Chest Index	0.964	1.010
Weight	59.9 kgm.	64.4 kgm.
Area	1.70 sq. m.	1.72 sq. m.
Lung Volume	3685 cc.	3710 cc.

Blood Chemistry.

Non-protein Nitrogen	34	mgm. per 100 cc.	36	mgm. per 100 cc.
Urea N.	15	mgm. per 100 cc.	16	mgm. per 100 cc.
Creatinin	2	mgm. per 100 cc.	1.7	mgm. per 100 cc.
Sugar	87	mgm. per 100 cc.	95	mgm. per 100 cc.
NaCl.	517	mgm. per 100 cc.		
Inorganic P.	4.8	mgm. per 100 cc.		

	Patient	Rowe & Lawrence Average
Calcium	10.3	
Wasserman	Negative	Negative in all Cases

Blood Morphology.

Haemoglobin	92%	90%
Erythrocytes	4.510,000	5.120.000
Color Index	1.	0.88
Leucocytes	8.800	8.000
P. M. N. Neutrophiles	28%	58%
Lymphocytes	60%	35%
Eosinophiles	2%	2%
Monocytes	9%	5%
Basophile	1%	0%

Respiratory Metabolism.

Basal Metabolic Rate	—22	—11
Blood Pressure:		
(a) Systolic	104	109
(b) Diastolic	66	65
Pulse Rate	70	67
Temperature	98.2	98
Alveolar CO_2	39	41

Galactose Tolerance.

	20 gms.	30 gms.

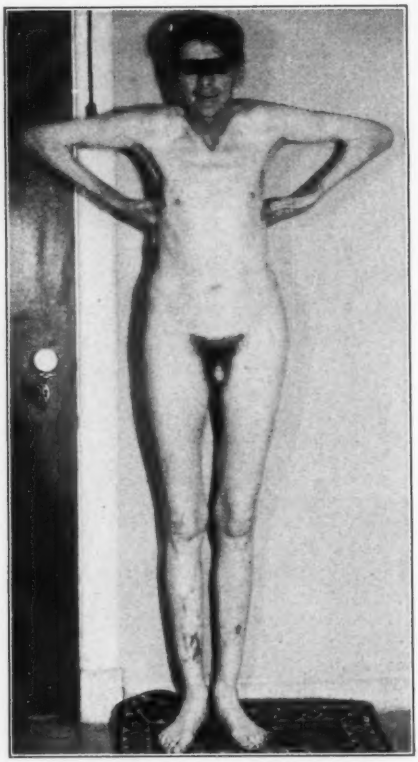
Urine.

	Patient	Rowe & Lawrence Average
24-hour Volume	1980 cc.	1100 cc.
Sp. G.	1015	1021
Total N.	12.0 gms.	11.34 gms.
Percentage Urea N. of Total N.	85.8	83.6
Creatine	0.058 gms.	

A fractional gastric analysis gave the normal type of curve with a maximum rise of free hydrochloric acid to 23 and a total acidity of 43 at the end of one hour.

A glucose tolerance test, using 105 gms. glucose, showed a fasting level of 0.087 with a curve showing evidence of normal tolerance. Urine collected at twenty-minute intervals during the test contained a trace of sugar at the end of forty minutes.

Radiological examination of the pelvis showed flaring of the ilia. The pelvis was definitely of the female type with a widening of the pelvic inlet which was circular in outline. There was no evidence of widening of the zone of proliferation at the epiphysis of the long bones. The skull showed a normal sella turcica with extreme thinning of the calvarium.



DISCUSSION

The marked abnormality in bony development as shown by the widening of the pelvis, the disproportionately long extremities and low sitting height index gave sufficient evidence that we were dealing with prepubertal hypo-function of the testes. One is inclined to discount the patient's story of testicular injury at the age of 32 as a contributing factor. He did not give a consistent story and is, as previously noted, trying to establish a case for the payment of an army pension.

The patient actually weighed 35 pounds less than his ideal weight. This degree of emaciation is not what one ordinarily associates with hypofunction of the sex glands. Tandler and Gross (1), however, in a study

of the physical changes in castrated Skopec men, pointed out that there is a lean as well as a fat type. Korenchevsky (4) in 1925 noted that 40 per cent of castrated dogs lost weight following the operation. He discussed the possible inter-relationship of the gonads with the other endocrine glands, particularly the thyroid, pituitary and pancreas. The persistent low basal metabolic rate in the patient would suggest hypothyroidism. Is it possible that the deprivation of the animal of the sexual hormone leads to an overactivity of the thyroid which accounts for the loss of weight and that later thyroid atrophy supervenes, causing metabolism to be carried on at a lower level? Rowe and Lawrence (5) report a basal metabolic rate of—30 in a man of 67, whose testicles had been removed 32 years previously. Korenchevsky (4) found that thin castrated dogs showed an increased nitrogenous metabolism and oxygen consumption above the control level. Two such animals showed an increased oxygen consumption of 14.6 per cent and 32.4 per cent on the 87th and 89th day, respectively, after operation. It would be of interest to know if this increased metabolic activity later disappeared in these animals since thyroid atrophy is a common finding in the castrate (1).

The close association between pituitary and gonads has long been clearly recognized. Biedl (6) observed hypertrophy of the pituitary in castrated animals. The abnormal length of the long bones which this patient shows so strikingly is due to delayed union of the epiphyses. The picture presented is so comparable to that found in the infantile type of pituitary hyperfunction resulting in gigantism that one must assume a related causative factor in spite of a normal appearing sella turcica.

Rowe and Lawrence (3) state that galactose tolerance in the male is not effected by the level of reproductive activity, being constant at 30 grams. We have not found this to obtain in this individual. The galactose test was carried out as described by Rowe (7). It was found that after the oral administration of 30 grams of pure galactose 0.721 gms. of sugar was excreted. After giving 20 gms. the excretion was 0.45 gms. Following a 10-gram dose no reducing substances were present in the urine. This test was repeated several times with similar results.

The comparison of the physical measurements with those of Rowe and Lawrence shows a close correspondence. It may be noted, however, that the sitting height index is considerably less than any reported in their series. The presence of relative lymphocytosis has been previously reported by Guggenheimer (8) in eunuchoids. The low systolic blood pressure was also a feature in the Rowe and Lawrence group.

SUMMARY

1. A case of a eunuchoid individual showing atrophy of the testes and prostate is reported.

2. The presence of marked skeletal changes, viz., widening of the pelvis, thinning of the calvarium, and disproportionate lengthening of the long bones with low sitting height index was noted.

3. The association of low basal metabolic rate, emaciation and changes in galactose tolerance is discussed.

My thanks are due to Dr. R. Proctor for the radiological investigation and the photograph.

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Abstract Department

The humoral source of the slight paralysis following adrenalectomy (Origine humorale de la parésie consécutive a la destruction des surrénales). Abelous, J. E. and H. Lassalle, Compt. rend. Soc. de biol. **103**: 475. 1930.

There was an increase in the nerve muscle chronaxie of frogs injected with blood from a frog deprived of his adrenals. This is evidence of the activity of the curari-like poison which is normally neutralized by the adrenal.
—J. C. D.

Effect of adrenin on the acid base balance and on ionized calcium (Influence de l'adrénaline sur l'équilibre acido-basique et le calcium ionique). Cahane, M. and I. Orasteanu, Compt. rend. Soc. de biol. **103**: 447. 1930.

Six experimental dogs were injected daily up to a period of six days. There was a reduction of the alkaline reserve and a tendency to increased calcium. These changes are similar to those produced by thyroid over-activity but more transitory.—J. C. D.

The effect of epinephrin in angina pectoris: with report of a case. Cottrell, J. F. and F. C. Wood, Am. J. M. Sc. **181**: 36. 1931.

In a single instance, subcutaneous injection of 1 cc. of 1 to 1000 epinephrin as a diagnostic test for angina pectoris resulted in a violent attack of substernal pain persisting for over eight hours; in collapse, unconsciousness, bradycardia, cessation of respiration, and a fall in blood pressure from 170/115 to 80/60; and in electrocardiographic changes suggesting added myocardial damage. Therapeutic use of epinephrin in patients who may possibly have angina pectoris requires great care; this caution probably applies likewise to ephedrin.—Authors' Summary.

Denervation of suprarenal glands. Crile, G. W., J. A. M. A. **96**: 219. 1931. (Proceedings of Western Surgical Association.)

In seventy cases, operations on the suprarenal glands have been performed for the purpose of controlling the kinetic activation. This series included cases of epilepsy, cardiovascular disease, neurasthenia, neurocirculatory asthenia, Raynaud's disease, diabetes, asthenia, recurrent hyperthyroidism and recurrent peptic ulcer. The results are sufficiently encouraging to warrant a further trial. The activity of the suprarenals is most effectually diminished by bilateral denervation. The point of view should be that of diminishing the excessive drive by one or several ways rather than by a single method. There is a physical mechanism the activity of which constitutes the restless, driving, worrying temperament, and with it a train of diseases. If by education, social adjustment and medical advice no improvement is realized, then surgery may enter by interfering with the mechanism of activation of the autonomic nervous system.

The stimulating influence of adrenin on muscle oxidation (Effet stimulant de l'adrénaline sur l'oxydation musculaire). Euler, U. v., Compt. rend. Soc. de biol. **103**: 445. 1930.

The oxidizing power of muscle preparations was tested by exposing them to an atmosphere containing only 2% oxygen. Adrenin lost its power to increase oxygen consumption when the muscle was deprived of its sympathetic innervation. The addition of glycerophosphate to the preparation restored this power.—J. C. D.

Influence of adrenalin and insulin on tissue oxidation (Studien uber die Beeinflussung der Gewebsoxydation durch Adrenalin und Insulin mit besonderer Berucksichtigung der Bedeutung der Innervation). Euler, U., Skand. Arch. f. Physiol. **59:** 123. 1930. Abst., Physiol. Abst. **15:** 391.

By use of the respirometer method (Barcroft-Warburg) the author confirms the findings of Ahlgren that adrenalin increases O_2 consumption in minced muscle and also in whole muscle. This increased oxidation, however, is only apparent when the O_2 content of the experimental vessel is between 2 and 10 p.c. Previous section of sympathetic nerves to a muscle prevented the typical increased oxidation with adrenalin, but section of the motor nerves was without effect. Adrenalin-ergotamine antagonism was shown by oxygen consumption in the minced muscle system. The author also confirms the observation that insulin in the presence of glucose increases tissue oxidation, but states that the increase is more evident with brain than with muscle. Increased oxidation with insulin is not dependent solely on glucose; glycerin can replace the latter, and the oxidation in this case shows many points of similarity with that when glucose is present. Muscle, the sympathetic nerve supply of which has been cut 2 days to 2 months previously, does not give the typical increased oxidation with insulin; section of the motor nerve is without effect. The antagonism between adrenalin and insulin in the presence of glucose was confirmed, and was shown to hold also when glycerin replaced glucose in the muscle mixture.

A further study of the hormone of the adrenal cortex. Hartman, F. A., K. A. Brownell and W. E. Hartman, Am. J. Physiol. **95:** 670. 1930.

Cats whose adrenals are removed in two stages survive from 6 to 11 days when untreated. Those injected with a small quantity of isotonic salt solution survived the shorter period. Increase in the interval between the operations, above a few days, does not decrease the survival period. Adrenalectomized animals show considerable loss in weight if they survive many days. Cortin, the hormone of the adrenal cortex which is essential to life, is carried down by the precipitated material formed when NaCl is added to the point of saturation or below. Adrenalectomized cats treated with an extract made from such a precipitate survived an average of 26.4 days. Heating the NaCl precipitate extract to 80°C. for five minutes destroys its potency. Precipitation of the protein in the NaCl precipitate extract by ethyl alcohol does not dimish the potency. A concentrated preparation of cortin can be made by extracting the cortex with ethyl ether which dissolves very little epinephrin. The ether is removed by distillation, the residue being extracted with warm 80% ethyl alcohol. Much inert material is removed by chilling and filtering. After removing the alcohol, the residue is taken up in water. The aqueous solution contains the cortin. This extract acts as a substitute for the adrenal cortex. Adrenalectomized cats are being kept alive in good condition indefinitely by its use. The growth of young rats whose adrenals have been removed has been maintained until the adult stage is reached by injecting the extract. Such rats behave normally in every way, even to raising litters. Cortin treated adrenalectomized cats eat well, gain in weight, play, fight and act like normals. Cortin lowers the blood urea when high. It increases the resistance to infection and to cold. It speeds the repair of injury and enables the animal to withstand operative or other trauma. By its use it is possible to remove both adrenals at one operation and maintain life indefinitely. Animals allowed to pass into the last stages of adrenal insufficiency which just precede death have been revived by cortin. A subject of Addison's disease with a systolic blood pressure of 50 mm. and a pulse of 120 per minute together with other characteristic symptoms has been revived by the use of cortin. Cortin is apparently not effective by mouth. When given subcutaneously one can begin to detect its effects in a few hours.
—Authors' Summary.

Studies on the adrenal cortex: III. The revival of cats prostrate from adrenal insufficiency with an aqueous extract of the cortex. Pfiffner, J. J. and W. W. Swingle, Am. J. Physiol. **96:** 180. 1931.

A method is described for the preparation of a potent extract of beef adrenal cortex, suitable for subcutaneous, intraperitoneal and intravenous use. It is practically free of adrenalin. When the extract is made up so that one cubic centimeter represents 30 grams of fresh adrenal cortex, the solid content is about 0.3% and the adrenalin content about one part in two million. This extract is sufficiently potent to make possible complete adrenal cortex

replacement therapy in acute adrenal insufficiency in experimental animals (cats).—Authors' Summary.

Addison's disease. Rowntree, L. G., C. H. Greene, W. W. Swingle and J. J. Pfiffner, J. A. M. A. **96**: 231. 1931. Abst., A. M. A.

The authors discuss their results in the treatment of Addison's disease, with various suprarenal preparations. Fifty-seven patients have been subjected to the so-called Muirhead treatment. Thirty-two cases are reported as temporarily benefited, and in twenty of these the immediate results were excellent. In some cases this period of improvement lasted for weeks, in others for months, and in ten cases for periods of from three to seven years. In contrast to this, the treatment was entirely without beneficial effect in twenty-five cases. The latter patients usually did not tolerate the epinephrine well, complained of increasing weakness and trembling and of nausea and vomiting, and in these cases there was a lowering, rather than an increase, in blood pressure. In general, with the Muirhead treatment, half of the patients showed some benefit, a third responded with results that were considered excellent, and a sixth were living after three years. The results of the Muirhead treatment may well be likened to those of treatment with roentgen rays or radium in carcinoma. With the application of radium marked temporary improvement is common, and remissions last for weeks, months and occasionally for years. And just as radium is curative in many cases of carcinoma of the cervix, so the Muirhead treatment is effective in certain types of Addison's disease. Radium is regarded usually as palliative in carcinoma; the Muirhead treatment is also palliative, but like radium it may also closely approach a curative measure. Various other products, prepared from the suprarenal gland or closely related to epinephrine either in their chemical structure or pharmacologic action, have been tried in the treatment of Addison's disease, including ephedrine and the cortical hormone of Swingle and Pfiffner. The effect of this last named preparation was observed on six patients. The amount of cortical hormone available for clinical use has been small and its delivery irregular, so that as yet it has not been possible to make a complete clinical study. The results to date, however, warrant this preliminary report. Their results convince the authors of the efficacy of this cortical hormone. The disappearance of anorexia, the increase of appetite to the point of hunger, the gain in weight, and the definite euphoria were striking in all cases. As long as the preparation could be administered, the results were all that could be desired. However, the supply of the preparation has been extremely meager and intermittent, so that it has not been possible to observe the results following consistent dosage and continued administration. Moreover, the first preparation used was not free from epinephrine and was irritating locally. The later supply, however, was almost, if not wholly, free from epinephrine, was suitable for intravenous administration, and was much less irritating when injected subcutaneously. Under ordinary conditions, the intravenous method of administration would seem to be preferable. The usual dose is from 10 to 20 cc. daily in divided doses, but 20 cc. has been given to a patient at one time without any undesirable reaction, and as much as 100 cc. has been given intravenously to dogs without any untoward effects. The immediate results in a crisis are excellent. The disease, however, is chronic, and it will be necessary for several years to elapse before a final appraisal can be made of the value of this cortical hormone in Addison's disease. The first three patients had previously been under the Muirhead treatment and all three stated that they felt better when this cortical hormone was given than with any treatment which they had received before. The return of appetite and the increase in weight have been the most striking effects witnessed by the authors in their entire experience with this disease. They are inclined to believe that the cortical hormone is as effective in meeting the crisis of Addison's disease as is insulin in diabetic coma. Although somewhat less prompt and dramatic in action, the results are almost equally striking. With unlimited supply of the hormone, it is possible that patients may be completely rehabilitated.

Adrenalin on isolated heart of castrated rats (Die Reaktion des isolierten Herzens der Kastrierten weissen Ratte auf Adrenalin). Sergijewski, M. W. and P. F. Teterin, Arch. f. exper. Path. u. Pharmakol. **149**: 211. 1930. Abst., Physiol. Absts. **15**: 469.

The isolated heart of the normal rat responds to the administration of 0.5 cc. adrenalin (1 in 1,000,000) with increased amplitude and slight accel-

eration. The heart of the castrated rat reacts with quickening of rhythm, diminished or unchanged amplitude. Larger doses give a normal reaction. Feeding the castrated animal for 1 to 3 months with dried testicle or prostate produces a normal response of the isolated heart to adrenalin, but feeding with powdered meat has no such effect.

Changes in sugar and lactic acid content of blood caused by burns. Slocum, M. A. and H. D. Lightbody, Am. J. Physiol. **96**: 35. 1931.

Studies have been made of the concentration of sugar and lactic acid in the blood of rabbits, burned with the suprarenal glands intact, and after the removal of the glands. The concentrations of both sugar and lactic acid were found to be increased. The increase of lactic acid was small and does not appear to account for the high sugar values. Twenty-four hours after burning, animals with the intact glands were found to have maintained the increased blood sugar while the lactic acid concentrations were reduced below the initial values. The studies indicate that increased activity of the suprarenals do not account for the increased blood sugar through lactic acid as an intermediate, or by a decreased rate of oxidation of the sugar.

—Authors' Summary.

Studies on the adrenal cortex. I. The effect of a lipid fraction upon the life-span of adrenalectomized cats. Swingle, W. W. and J. J. Pfiffner, Am. J. Physiol. **96**: 153. 1931.

By use of an alcoholic-benzene extraction process a crude lipid fraction of the suprarenal cortex of beef has been obtained, which when injected subcutaneously will prolong considerably the survival period of bilaterally adrenalectomized cats. The cortical hormone is stable in ethyl alcohol for a period of at least two weeks, and the crude lipid fraction when prepared in oil retains its potency for about three weeks when kept at 60°C. The active lipid fraction is not adrenalin-free. In so far as the writers are aware, this is the first conclusive demonstration that the hormone of the suprarenal cortex which is essential for the maintenance of life can be extracted with lipid solvents.

—Authors' Summary.

Studies on the adrenal cortex: II. An aqueous extract of the adrenal cortex which maintains the life of bilaterally adrenalectomized cats. Swingle, W. W. and J. J. Pfiffner, Am. J. Physiol. **96**: 164. 1931.

Fractionation studies of a crude lipid extract obtained by alcoholic-benzene extraction of the suprarenal glands of beef were undertaken. The criterion of activity employed was the effect upon the life-span of bilaterally adrenalectomized cats. The following facts were obtained: The acetone soluble fraction contains the cortical hormone and is highly active, but offers serious difficulties in administration. The acetone insoluble fraction is inactive since it is entirely without beneficial effect upon the life span of adrenalectomized animals. The petroleum-ether-soluble fraction following a single distribution of the acetone-soluble fraction between petroleum-ether and 70% alcohol contains a small amount of the hormone. After four such distributions the petroleum-ether fraction is without activity. The alcohol soluble fraction obtained after distribution between petroleum-ether and 70% alcohol contains the hormone of the suprarenal cortex. This fraction will maintain adrenalectomized cats indefinitely in normal health, so long as the extract is administered. Following cessation of treatment (an arbitrarily selected period of 100 days was used) such animals die within a short period with typical symptoms of adrenal insufficiency. Potent extracts have been prepared from adrenal cortex stored in alcohol at room temperature for periods of two to three weeks. No deterioration in activity was observed in active fractions stored in alcohol or benzene at 8°C. from four to six weeks. Active fractions can be safely stored in acetone for several days. Our tests indicate that there is no loss of activity in aqueous extracts in seven to fourteen days when stored at 8°C. without a preservative. We have preferred to use fresh extracts each week. Observations on keeping qualities of aqueous extracts with and without preservatives will be reported later. The aqueous extract is not adrenalin free. The scheme of fractionation eliminates on an average about 99.6% of the adrenalin present in the fresh cortical tissue. The ex-

tract is protein free. The writers prefer to use the term cortical hormone pending definite knowledge of the chemical nature of physiological function of the hormone or hormones involved.—Authors' Summary.

Biochemical studies on the effect of adrenalin upon the nitrogen metabolism of rabbits. Watkins, O. and G. V. S. Smith, Am. J. Physiol. **96**: 28. 1931.

Intramuscular, subcutaneous and intraperitoneal injections of 0.1 mgm. doses of adrenalin result in marked rises in blood sugar and later in the urea of the blood. There is no retention by the kidneys, as shown by urine analyses during prolonged experiments in which repeated injections of adrenalin were given. There is, in fact, some indication of an increased excretion of urea. It is concluded, therefore, that the rise in blood urea is a result of some catabolic action of adrenalin upon protein metabolism. The intravenous administration of glucose after the injection of adrenalin does not affect the rise in urea. The administration of glucose and insulin after adrenalin exaggerates and prolongs the urea rise. These experiments were carried out in connection with a previous report by the authors (Am. J. Physiol. **94**: 586. 1930) in which it was shown that corpus luteum and adrenalin have identical effects upon the blood chemistry of rabbits. It is concluded that these two secretions have a catabolic action upon the proteins as well as the carbohydrates and it is suggested that this finding may present new possibilities as to the mechanism of the action of adrenalin.—Authors' Abst.

Genitodystrophic geroderma (Geroderma genito-distrofico). Bardisian, A., Riv. d. clin. pediat. **28**: 457. 1930. Abst., J. A. M. A. **95**: 899.

Bardisian recalls that, although Souques and J. R. Charcot published in 1891, under the name of cutaneous geromorphism, a number of observations, the merit of having first described genitodystrophic geroderma belongs to Rummo and Ferrarinni (1897). They introduced the study of diseases with pluriglandular symptoms and outlined the pluriglandular treatment. The characteristics of these patients are so evident that they can be recognized at a glance, without even analyzing the genitalia; for, while they present an aged appearance, they are still young. Pluriglandular lesions have always developed at an early (prepubertal) age. The author describes (three illustrations) a child, aged 14, who had all the appearance of an aged person (the condition dating from his sixth year) and who presented all the characteristic symptoms of the disease that Rummo and Ferrarinni were the first to describe.

Hormones in cancer I. The effect of ovarian, splenic, and adrenal extracts upon rat sarcoma No. 10. Bischoff, F. and I. C. Maxwell, J. Pharmacol. & Exper. Therap. **40**: 97. 1930.

Rats with R-10 sarcoma received subcutaneous injections of various preparations. Follicular extract (Allen-Doisy), corpus luteum (H. W. & D.), splenic extracts prepared by the authors and eight adrenal extracts were without effect in inhibiting growth of tumors. The follicular extract, corpus luteum, the Coffey-Humber and Eaton adrenal extracts and two other adrenal extracts prepared by the authors produced early liquefaction of the tumors. The sources or methods of preparation of all extracts are described in detail.—C. I. R.

Obesity is of mixed origin, the endogenous and exogenous factors being intimately connected (El factor pancreatico enlas obesidades exogenas y endogenas). Bonilla, E., Siglo med. **85**: 125. 1930.

It has been found experimentally that a diet rich in meat produces intense lesions in the thyroid and testes. Some authors now admit the existence of a pancreatic form of obesity. Previously this obesity was explained on an insulin insufficiency, but later on a basis of carbohydrate metabolism. The remarkable effects of insulin in fat-reduction, and descriptions of hyperinsulin syndromes are responsible for the change of ideas. At present Falta maintains that only individuals with a normal insulin function can be fattened, and that in some cases the cause of obesity could reside in an inadequate response of the isles of Langerhans to alimentary stimulation. The exogenous obesity through excessive food could function through an endogenous-pancreatic mechanism. The author cites a case of colossal obesity clearly of exoge-

nous origin. There did not exist a single thyroid disturbance, nor hypophyseal or ovarian defect. The author holds that insulin has a position of prime importance in cases where the process of assimilation is increased. Generally there is a greater secretion of insulin by the effect of alimentary stimulation (exogenous obesity), but many facts point to the pancreatic activation by an indirect insulinism in endo-obesity, in some cases possibly connected with the thyroid, hypophysis, or testes. In admitting a primary insulin obesity it is necessary to proceed with caution.—G. M.

The effect of insulin and other endocrine extracts on the cholesterol content of tissues. Chamberlain, E. M., J. Physiol. **70**: 440. 1930.

An effort was made to determine the effect of endocrines on cholesterol metabolism. Dried thyroid extract, pituitrin and insulin were used. The latter alone produced decrease of the cholesterol content of the adrenals, which was less pronounced if hypoglucemia was prevented by glucose. Other organs were not affected.—C. I. R

The relation of the endocrine glands to the growth and distribution of hair. Cooper, A. K., Arch. Dermat. & Syph. **21**: 1007. 1930. Abst., Arch. Neurol. & Psychiat. **25**: 191.

The distribution of the hair, as to both site and amount, is so easily studied that the establishment of any constant relationship between the pilary system and other functions of the body would be of great value. The endocrine glands offer the most promising field for this study. Cooper, reviewing the literature and conducting experiments of her own, establishes the following relationships: A reduction in parathyroid activity is associated with a scanty growth of hair; a reduction in pituitary function usually means loss of hair everywhere except on the scalp. On the other hand, hyperpituitarism is responsible for increase in the thickness and the area of distribution of the hair. No conclusive evidence has been presented to relate the activity of the thymus with the pilary system. It is known that hypotrichosis is associated with reduced functions of the cortex of the suprarenal glands, and hypertrichosis with excessive function of this structure. With destruction of pineal activity early in life, abundant growth of the hair is the rule. There is much confusion about gonadal relationships in the modifications of the development of the hair, although it seems fairly clear that castration is associated with a reduction in the area of the hair and with a feminine distribution. There is an uncertain degree of hypertrichosis in diminished ovarian activity. In the case of the activity of the thyroid, the relative hairlessness of the cretin and the hairiness of the patient with acromegaly are well known.

Changes in the thyroid gland in fluorine poisoning (Altération de la glande thyroïde dans l'intoxication fluorée).

Gross changes in the hypophysis in fluorine poisoning (Les altérations macroscopiques de l'hypophyse dans la fluorose). Cristiani, H., Compt. rend. Soc. de biol. **103**: 554; 556. 1930.

Guinea pigs were exposed to fluorine for three to twelve weeks. The thyroids were enlarged with proliferation of the parenchyma and the pituitaries reduced to about 80% of their normal thickness.—J. C. D.

On the production of typhoid antitoxic substance and its relation with hormones. Katabuchi, H., Acta. Med. Keijo. **12**: 1. 1929.

Numerous experiments were made upon mice to determine the percentage of survival after the administration of typhoid toxin alone or with the serum of rabbits and in combination with suprarenal and various other cortical extracts. The method of making the extracts is not stated. It was found that the proportion of survival was 4.4% with typhoid toxin alone, and this proportion was increased to 10% by adding the serum of the normal rabbits, and to 20.4% by adding the serum of immunized rabbits. For convenience the typhoid antitoxic substance is referred to as (T. A. S.). After injection of suprarenal cortex extract the production of T. A. S. in the blood serum was increased slightly in the normal rabbit and in a remarkable manner in the

immunized rabbit. The T. A. S. that was produced after the injection of suprarenal cortex extract was able to neutralize 2-3 times the lethal dose of typhoid toxin. On the other hand, this T. A. S. did not counteract the toxin of Bacaillus dysenteriae (Shiga type), nor of B. coli, nor of B. tetani. It was shown that the production of T. A. S. by injection of suprarenal cortex extract is based upon a hormonal mechanism; since for its production the presence of the hormones of parathyroid and thyroid glands are necessary, but the thymus and testicle are not essential. The production of T. A. S. that occurred after the injection of the extract of parathyroid, thyroid, thymus and testicle was lôwer than when the suprarenal cortext substance was used, and further in cases injected with the extract of muscle, kidney and casein, this substance was not produced at all.—R. G. H.

On the degree of oxidation going on within the animal body under several conditions. Kimura, H., J. Biochem. **12**: 351. 1930.

A modification of the Muller Vakat-oxygen method is presented and discussed. In cats it was found that extirpation of the thyroid gland induces a decrease in amount of oxygen consumption. The degree of oxidation, however, is not much affected. The feeding of the thyroid gland increases the amount of oxidation, while the degree of oxidation is decreased far below normal. Suprarenal extirpation results in the decrease in both the amount of nitrogen and in the total metabolism. The degree of oxidation seems, however, not much influenced.—R. G. H.

Further observations on the depressor substance in brain tissue. Major, R H. and C. J. Weber, J. Pharmacol. & Exper. Therap. **40**: 247. 1930.

The depressor activity of brain extract is not due to histamine, choline or acetyl choline.—C. I. R.

The endocrine influence in sterility. Rowe, A. W., J. A. M. A. **95**: 1219. 1930.

A series of sterile marriages has been reported with regard to the coexistence of various diseases. The marriage histories of a group of normal, healthy, pregnant women have served as controls. It appears that endocrine disorders do not result in a decreased number of marriages. The percentage of sterile marriages is highest in those showing ovarian disease, next highest in thyroid, and lowest in pituitary disorders. In the non-endocrine group studied infertility was definitely less frequent than among those having endocrine disease. Even with the nonendocrine group the incidence of infertility is double that usually regarded as normal for the community.

—Author's Summary.

Studies of the pulse and blood pressure in catatonic patients in a normal state and after the administration of drugs. Walther, F., Arch. f. Psychiat **89**: 377. 1930. Abst., Arch. Neurol. & Psychiat. **25**: 187.

The author reports investigations of the pulse and blood pressure and their relationship to one another in normal as well as in catatonic persons. These studies are supplemented by investigations of the same type in the same persons after the administration of different drugs. Four normal persons were studied and the conclusions reached were that a pulse of 60 corresponds to a systolic pressure of from 115 to 135 and diastolic of from 60 to 80, with a pulse pressure of from 50 to 70. A pulse of 70 normally corresponds to a systolic blood pressure of from 120 to 145, a diastolic pressure of from 60 to 90 and a pulse pressure of from 50 to 80. Drugs that cause an increased irritability in the sympathetic system will bring about an increase of the pulse rate and of the systolic pressure with a decrease of the diastolic pressure, thus causing an increased pulse pressure. On the other hand, an increased irritability of the parasympathetic will cause a decrease both in pulse rate and in pulse pressure. Atropine first causes stimulation of the vagus but later paralysis. Pilocarpine is a sympathetic stimulant. Epinephrine acts mostly in a similar fashion. Pituitary extract is a vagus stimulant and testicular extract acts in the same way; so does thyroxin to a certain extent, although the author states that other observers found this drug to have the opposite effect. The effects of drugs in a normal person depend much on the type of personality. In a sympatheticotonic person, drugs that stimulate the sympathetic system

will have more effect than those that stimulate the vagus, and vice versa Catatonic patients (five cases were studied) differ from normal persons in a disturbance of the relationship of the three factors, in the usually vagotonic reaction type and in the lability of all three factors. These differences are marked in catatonic stupors. The effect of drugs in the catatonic patient is similar to that in normal persons.

Ovarian graft in normal rats (Injerto de ovario en ratas enteras). del Castillo, E. B. and J. Calatroni, Rev. Soc. argent. de biol. **6**: 341. 1930.

Intrarenal implantation of ovarian tissue "takes" in 100% of cases when the recipient is a castrated female. In normal females only 41% "take" (7 out of 17); in these no corpora lutea were observed, and only in one case was a ripe follicle seen. Therefore when functioning ovaries exist in the organism it is less easy to graft a third ovary and this last shows signs of diminished activity in those cases in which the graft "takes."—J. T. Lewis.

The corpora lutea of the mouse, with special reference to fat accumulation during the oestrus cycle. Deanesly, R., Proc. Roy. Soc. (B.) **106**: 578. 1930.

The work was done on the ovaries of 50 mice, 11 being unmated, 10 pseudo-pregnant, 17 pregnant and 12 in the state of post parturition. The lutein cells in the corpus luteum of pseudo-pregnancy differ from those in the corpus luteum of ovulation in the slower rate at which they accumulate fat, in their slightly larger size and the smaller nuclei. During pregnancy the growth of the corpus luteum can be divided into three periods. In the first period, which lasts until the eighth day after copulation, the corpus luteum has practically no fats or lipoids in the cells. During the second period, the corpus luteum reaches its maximum dimensions (nearly 1 mm.). In the third period (from the eighteenth day of pregnancy) the corpus luteum accumulates fat and decreases in volume. After parturition the corpora lutea may persist for a considerable time as they do in the rat. The cells in the corpora lutea of lactation which are formed at post-partum ovulation remain small and fat-free for 8 days. The corpora lutea of lactation approximate the corpora lutea of ovulation and pseudo-pregnancy in size. The rate of fat accumulation is slower since these corpora lutea of lactation have a longer functional life than those of pseudo-pregnancy.—E. L.

Studies on ovulation. III. Effect of vaginal anaesthesia on ovulation in the rabbit. Fee, H. R. and A. S. Parkes, J. Physiol. **70**: 385. 1930.

Vaginal anaesthesia by novocain or "Percain" does not inhibit copulation or ovulation.—C. I. R.

Formation of adenomatous mammary glands following prolonged injections of folliculin (Production de formations adénomateuses mammaires par des injections prolongées de folliculine). Goormaghtigh, M. and A. Amerlinck, Compt. rend. Soc. de biol. **103**: 527. 1930.

Twelve sixty-day mice were injected daily with six rat units of folliculin over periods varying from a week to nine months. After four weeks the mammary glands become adenomatous with distended acini and ducts. This is explained by the prolonged action of the corpora lutea whose normal life is increased by folliculin injections. In cases where the dose of folliculin was too great for corpora to form, and in spayed mice, no adenomata developed.
—J. C. D.

Oestrus and pseudo-pregnancy in the ferret. Hammond, J. and F. H. A. Marshall, Proc. Roy. Soc. (B.) **105**: 607. 1930.

The period of anoestrum in the ferret extends from August to the following March or April. During the remainder of the year the female remains in heat (if unmated). There is a very marked swelling of the vulva (about 50 times in size) and congestion of the uterus during this period. Pseudo-pregnancy induced by mating with a vasectomized male lasts 5½ to 6 weeks. Ovulation takes place only after copulation. After mating, the vulva gradually decreases in size until it is nearly or quite as small as during anoestrum. During anoestrum the follicles in the ovaries are small, but during heat the

follicles enlarge so that it is possible to see them with the naked eye. The corpora lutea formed from the ruptured follicles are functional until the end of pseudo-pregnancy or pregnancy. During lactation they rapidly atrophy. In the anoestrum the uterus is small and anemic. When oestrus takes place the uterus enlarges, the mucosa is thrown up into folds and the surface glands hypertrophy. The hypertrophied glands degenerate and are cast off at about 5½ weeks. Regeneration takes place during the eighth week and the animal is again in heat. The uterine changes during pregnancy are similar. The hypertrophy of the mammary glands during pseudo-pregnancy and pregnancy was similar. The growth of the mammary gland is caused by the corpus luteum.—E. L.

The anterior lobe and menstruation. Hartman, C. G., W. M. Firor and E. M. K. Geiling, Am. J. Physiol. **95**: 662. 1930.

Injections of Allen-Doisy hormone (e.g., in the form of Amniotin Squibb) have been known to cause bleeding in female monkeys, whether normal or castrated. It is here shown that this also occurs consistently in baby monkeys 1300 to 1700 grams in weight, about a year old and 2½ to 3 years before the menarche—that is, corresponding to a human child three or four years of age. That this effect is not a direct one is shown by the fact that hypophysectomy abolishes the effect. But bleeding occurs in hypophysectomized as well as normal animals by injection of anterior lobe extracts or by implants of the fresh gland. This is interpreted as a direct effect. A physiological basis of uterine bleeding is, therefore, for the first time demonstrated and the menstruation problem is lifted from the realm of theory and conjecture. It seems reasonable to postulate a separate anterior lobe hormone as the direct cause of bleeding, since it is here demonstrated that the bleeding is independent of the follicle stimulating effect of Smith and Engle and the luteinizing phenomenon of Evans and Simpson and other influences attributed to the gland. With the treatments here outlined bleeding may result from a uterus that shows not the slightest macroscopic change. Hence the threshold for bleeding is far below that causing "oestrous" changes (growth, edema, congestion) in uterus or ovaries. This has adaptive significance for the prime and original function of the bleeding is that of supplying blood cells (perhaps for iron) directly to the embryo in early pregnancy; "oestrous" changes would be disastrous to the continuance of pregnancy. Since uterine bleeding may be caused so much more readily than hyperplasia of dormant reproductive tract and ovaries, the gynecologist must determine what benefit the patient receives from a mere bleeding without the usual concomitant "oestrous," not to mention pregravid changes.—Authors' Summary.

The relation of ovarian hormones to electromyographically determined Achilles reflex time. Herren, R. Y. and H. O. Haterius, Am. J. Physiol. **96**: 214. 1931.

Determinations on sixteen female rats through thirty oestrous cycles showed a long Achilles reflex time during the oestrous period and a short Achilles reflex time during the dioestrous period. Determinations on castrates indicated a lengthened Achilles reflex time following injection of extract of follicular fluid and a shortened Achilles reflex time consequent to injections of extract of corpus luteum, whereas controls displayed no significant change. The pregnant animal was characterized by a gradual decrease in Achilles reflex time until the tenth or eleventh day of term, at which a gradual increase in reflex time appeared, culminating in the extreme long reflex time of parturition. Pseudo-pregnant animals showed a gradual decrease in Achilles reflex time corresponding in length to the functional life of the corpora lutea of pregnancy. It is concluded that the sex hormones play a vital part in the interaction of the various neural levels, either through direct influence on nervous tissues of higher levels, or indirectly through other connections with the higher levels. —Authors' Summary.

The female hormone (menformone) in male organs; some views on specificity. de Jongh, S. E., E. Laqueur and E. Dingemanse, Arch. néerl. de physiol. **14**: 276. 1929. Abst., Chem. Absts. **24**: 5832.

Menformone was readily obtained from male urine, by benzene extraction, saponification and solution of the product in water. The potency was 1 mouse unit per 0.02 mgm. This material was injected into a variety of animals. It

caused a marked increase in the size of female genitals and mammary glands, had an antimasculine influence, stimulated vital activities of females and was entirely non-toxic. The apparent differences in effect on males and females are probably due to the higher concentration in the latter. Two phases of specificity are emphasized, one based upon characteristic properties and the other on origin.

Feathers as indicators of concentration of female hormone in the blood. Juhn, Mary, G. H. Faulkner and R. G. Gustavson, Proc. Soc. Exper. Biol. Med. **27**: 1078. 1930.

Feathers formed on Brown Leghorn capons receiving regular effective daily injections of female hormone (oestrin) are completely female in character. If injections are given intermittently, then feathers with alternate bars of female and male type are formed, the width of the bars varying with the size and the number of injections. In any one bird the induced female bars are broader in the saddle than in the breast feathers, and since the rate of growth of the female bar is approximately the same in both, this indicates that the concentration of the hormone in the blood was above the saddle threshold for a longer time than it was above the breast threshold.—R. G. Gustavson.

The effects of simultaneous injections of the female and male hormones in capons. Juhn, M., F. D'Amour and E. B. Womack, Am. J. Physiol. **95**: 641. 1930.

The effects of combined injections of the female and male hormones and of alternate injections on successive days were studied in adult capons. The birds receiving the simultaneous injections developed female plumage and male head furnishings. The same results were obtained when the hormones were mixed "in vitro" for twenty-four hours and forty-eight hours, respectively, previous to injection. When the hormones were administered in the same concentration but on alternate days female plumage was not obtained and the head furnishings showed only very slight growth. There are no indications of an antagonism between the chemically prepared sex hormones with the preparations used in the adult capon, neither is there an intensification of the action of one hormone in the presence of the other.—Authors' Summary.

Studies on metabolism. VIII. The effect of estrin injections on the basal metabolism, uterine endometrium, lactation, mating and maternal instincts in the adult dog. Kunde, M. M., F. E. D'Amour, A. J. Carlson and R. G. Gustavson, Am. J. Physiol. **95**: 630. 1930.

The basal metabolic rate in normal dogs is neither lowered nor elevated as a result of subcutaneous injections of female sex hormone (estrin). Many tests near the lower limit of normal variation occur, so that the average over a period of daily injections may be slightly (2%) below the average for a control period. Congestion and enlargement of the external genitalia, hemorrhagic discharge from the vagina, hypertrophy of the uterine endometrium with histological evidence of secretory activity, and evocation of the mating instinct follow the administration of female sex hormone in the normal and castrate bitch. Hyperplasia of the nipples and slight palpable enlargement of the mammary glands occur in all dogs, and copious lactation and evocation of the maternal instinct in one dog followed the subcutaneous injection of estrin.—Authors' Summary.

Concerning the sexual significance of the hair of the head and the human "fine hair" (Sobre el significado sexual del cabello y el vello humanos). Marañon, G., Arch. de med. cir. y espec. **29**: 635. 1928.

It is well known that the distribution of the fine hair on the trunk and limbs, and especially the hair of the head, constitutes a typical external sign for sex distinction. Each sex has its peculiar pillosity. It was observed in a case of inversion (morphological and psychical simultaneously) that the pillose character was of the opposite sex. The author has studied the pillose character in a great number of patients of both sexes, chiefly as related to hair arrangement on the forehead of the male after puberty. In the female as in the prepubertal stage, i.e., the frontal-parietal line is inferio-concave while in the male it is inferio-convex. In a similar manner there is a difference in the hair on the

neck, terminating in the female in a neat line with constant lateral prolongations and at times a central one. In man this disposition disappears by a diffuse increase of hair in the occipital region disappearing either irregularly or following a regular line as in a typical case.—E. B.

Threshold relationships of testis hormone indicators in mammals; the rat unit. Moore, C. R. and T. F. Gallagher, J. Pharmacol. & Exper. Therap. **40:** 341. 1930.

In point of sensitivity the mammalian testis hormone indicators rank in the order (a) spermatozoon motility test, (b) prostate cytology test, (c) seminal vesicle, Cowper's gland, and vas deferens tests, (d) electric ejaculation test. The rat unit of male hormone is defined in terms of dosages that effect complete replacement of the internal secretion of the testis. Approximately one-twentieth of a rat unit is detectable by the prostate gland and one-sixth of a unit by the seminal vesicles, Cowper's gland and vas deferens. One rat unit is approximately the equivalent of six bird units, as defined by Gallagher and Koch.—Authors' Summary.

The treatment of patients with Addison's disease with the "Cortical Hormone" of Swingle and Pfiffner. Rowntree, L. G., C. H. Greene, W. W. Swingle, and J. J. Pfiffner, Science, **72:** 482. 1930.

The authors report very striking clinical success with Swingle and Pfiffner's preparation of cortin. The daily dosage was the amount of cortin derived from 50 ounces of fresh beef adrenal cortex. The detail of preparation is added that by the use of permutit on the alcoholic solution of the cortin, the adrenin, most of the contaminating pigment and much inert material can be removed.—R. G. H.

Information concerning the endothelsymptoms for the diagnosis and therapy of the endocrine disorders; especially ovarian insufficiency (Die Bedeutung des Endothelsymptoms für die Diagnostik und Therapie endokriner Storungen, insbesondere der ovariellen Insuffizienz). Seyderhelm, R. and M. Heinemann, Deutsche med. Wchnschr. **56:** 860. 1930.

The authors report that the Rumpel-Leede phenomenon, the "endothelsymptom," is useful in the judgment of ovarian hormone content of the blood. The phenomenon is elicited by the application to the arm of constricting pressure ± 20 mm. above the existing diastolic level. This, in a positive case, causes the appearance of minute petechiae. It was found that the Rumpel-Leede phenomenon is present when ovarian hormone is lacking and that the extent of this reaction parallels closely the decrease in ovarian hormone content of the blood. During menstruation and at the climacteric when there is a deficiency of ovarian hormone, the Rumpel-Leede phenomenon is present, but during pregnancy when the blood is richest in that substance, the phenomenon is never present unless there be coincident infection or toxic conditions. Under these circumstances, injection of ovarian hormone has no effect in making the Rumpel-Leede phenomenon negative so that the authors conclude that the mode of action of the Rumpel-Leede phenomenon through ovarian insufficiency is quite different from that through infection or intoxication. The only other endocrine gland preparation found to influence the Rumpel-Leede phenomenon was that of the thyroid which, when administered to obese postclimacteric women, had the same effect as the ovarian hormone. More than 1000 trials of the Rumpel-Leede phenomenon were made. The efficacy of ovarian hormone therapy, as judged by this phenomenon, was corroborated only by the subjective reaction of the patient.—Ruth M. Thompson.

A biochemical investigation into the function of corpus luteum. A study of blood sugar and non-protein nitrogen changes in rabbits after the administration of corpus luteum. Smith, G. V. S. and O. Watkins, Am. J. Physiol. **94:** 586. 1930.

Marked rises in blood sugar and in blood urea were found to follow the intraperitoneal injection of a lipoidal extract of corpus luteum, prepared according to the method of Corner and Allen, into normal doe rabbits that had recently been served or had delivered young. Spayed does and bucks did not

give any blood sugar or urea changes after injection normally, but if previous to giving the corpus luteum these animals were primed with folliculin, typical reactions followed. It was indicated that the urea rise was not the result of kidney damage. The interesting finding was made that epinephrine always causes in rabbits exactly similar blood sugar and blood urea curves. This suggests that corpus luteum under certain physiological conditions has some effect upon the sympathetic nervous system, either directly or through the adrenal medulla. It seems possible that the biochemical changes observed following the injection of single large doses of corpus luteum extract may be an exaggeration of a normal catabolic action of this gland. This effect would be in keeping with the importance of the corpus luteum for the implantation and nourishment of the ovum.—O. Watkins.

The heart rate after sympathectomy and vagotomy and the blood sugar as affected by posterior hypophyseal extracts (pitressin and pitocin). Bacq, Z. M. and S. Dworkin, Am. J. Physiol. **95**: 605. 1930.

In normal cats pitressin, injected intravenously, causes a prompt reduction in heart rate (confirming Gruber's observations). Pitocin has little effect. In surviving vagotomized cats, pitressin reduces the heart rate, but to a level still far above the average basal rate for a normal animal. In cats surviving excision of both sympathetic chains, the action of pitressin upon heart rate is dependent upon the presence or the absence of (central) vagus innervation to the heart. Slowing occurs when the vagi are present; marked acceleration when these nerves have been sectioned. Both pitressin and pitocin, given intravenously, cause a prompt rise in blood-sugar concentration. The hyperglycemia may last as long as two hours. In sympathectomized cats the glycemic effect of pitressin is somewhat less than in normal animals, but not markedly so.—Authors' Summary.

The ratio between nucleus and cytoplasm in the cells of the cat's hypophysis (Le repport nucléo-plasmatique dans les cellules de la glande pituitaire chez le chat). Collin, R., Compt. rend. Soc. de biol. **103**: 599. 1930.

The nucleus forms about 27% of the entire cell in chief cells, eosinophiles and cells of the pars intermedia. In the tuberalis, 35% of the cell is nucleus and in the acidophile cells only 22%. Since the relative size of the nucleus decreases with the age of the cell, those of the tuberalis are youngest, while the acidophiles are old cells, which may be derived from any of the other types.—J. C. D.

Actions of hormone of anterior lobe of hypophysis. Falta, W. and F. Hogler, Klin. Wchnschr. **9**: 1807. 1930. Abst., J. Am. M. Ass. **95**: 1874.

Falta and Hogler investigated the actions of the hormone of the anterior lobe of the hypophysis. First they tested the influence of a hypophyseal preparation on the production of body heat. In the majority of cases they found a considerable reduction, not only in the cases with a normal basal metabolism. Further, the effect on the carbohydrate metabolism was investigated. It appears that the hormonal preparation influences the carbohydrate metabolism only when insulin is present. It is not certain, however, whether this applies to all cases. In persons without diabetic symptoms, who were given insulin in combination with a cure of forced feeding, there was no marked modification of the carbohydrate metabolism in the sense of hypoglycemic manifestations. On the contrary, in some instances it appeared as if an increased sensitivity to insulin developed. The authors further investigated the action of the hormonal preparation of the anterior lobe of the hypophysis on the process of growth and on the genitalia. In two cases of infantilism it was found that growth could be stimulated with the hormonal preparation; however in two cases of eunuchoidism the growth was not simulated. With regard to the problem of whether all the actions of the extract of the hormone of the anterior lobe of the hypophysis are produced by one elementary substance or whether the extract contains several hormones, the authors state that most investigators are now inclined to believe that the anterior lobe produces several hormones. They themselves did not investigate this problem but they found that the substance extracted from the urine of pregnant women influences the metabolism, the growth and also the genital sphere.

Hydatidiform mole as a cause of positive reaction in Aschheim-Zondek pregnancy test. Fanz, J. I. and E. S. Gault, J. Lab. & Clin. Med. **16**: 27, 1930.

In the study of a series of cases to ascertain the accuracy of the test, Fanz and Gault obtained the urine of a woman three days after she had expelled a hydatidiform mole. Diagnosis of the mole was confirmed by microscopic study. A definite positive Aschheim-Zondek test was obtained. The originators of the test have shown that the positive reaction is due to excessive anterior pituitary hormone produced physiologically during pregnancy, and eliminated in the urine in detectable amounts, from the first month until about one week after delivery. As there was no foetal formation in this case, the authors attribute the pituitary hyperfunction of the woman (pituitary secretion demonstrable in her urine) to the stimulation of her pituitary gland by the tissue cells of the chorion or decidua, rather than to the growing embryonal mass. On examining the curve of pituitary secretion during amenorrhea of the mother (Aschheim-Zondek), we find the anterior pituitary hormone rising abruptly in amount during the first month, remaining more or less fixed during the next five lunar months, falling gradually during the later four months and then more abruptly for a week following delivery. This curve is practically coincident with the development of trophoderm and its derivative, the chorion, and in its later half of declination is coincident with the disappearance of Langhan's cells (from the fifth month on). Can it be that Langhan's cells with their trophodermal precursors through their products stimulate the anterior pituitary body to hypersecretion during pregnancy? On studying placental development with special reference to syncytium, we find it apparent at the third month, reaching its full development (except as to size) at the fourth month, and continuing its development throughout pregnancy. It seems that syncytial development is practically portrayed by the curve of ovarian secretion to the extent that it would suggest an effect on the ovarian hormone (liberation from the corpus luteum of the ovary). The decidual proliferate of the uterus can hardly be considered a producer of hormone to the anterior pituitary, due to the fact that it is inherently maternal tissue from the start. Following this deduction it would seem that the anterior lobe of the hypophysis acts as a co-secretor organ to the growing placental proliferate (possibly layer of Langhan's), causing anterior pituitary activity rather than the cells of the fetus per se.

Inasmuch as the patient gave no evidence of breast hypertrophy, it would seem that the pituitary hormone has no effect on the breasts of the female. This is in keeping with some unpublished findings of one of the authors, who found no effect on the lactating and prelactating breasts following administration hypodermatically of pituitrin, during the period of two weeks following labor.—J. I. Fanz.

Powdered anterior lobe on the ovary (Die Wirkung von Hypophysenvorderlappenpulver auf das Ovarium). Loeser, A., Arch. f. exper. Path. u. Pharmakol. **148**: 377. 1930. Abst., Physiol. Absts. **15**: 467.

Fresh anterior lobes were dried by mincing in acetone, fresh portions of acetone being used several times. The material was then powdered in an agate mortar and stored in an evacuated desiccator over P_2O_5. When 0.06 gm. of this material was rubbed up with saline and administered in 6 injections (during 48 hours) to a young rat, sexual changes were seen in 4 days. The uterus was thickened, congested, and full of secretion, and the ovaries contained corpora haemorrhagica. Corpora lutea were also found in the ovaries on histological examination.

Powdered anterior lobe and the ovary (Hypophysenvorderlappenpulver und Ovarium. I. Mitteilung: Qualitative Wirkung). Loeser, A., Arch. f. exper. Path. u. Pharmakol. **150**: 106. 1930. Abst., Physiol. Absts. **15**: 467.

Powdered anterior lobe injected in a saline suspension into the peritoneal cavity of immature rats and rabbits causes growth of follicles, follicle ripening, and lutein formation, just as does the transplantation of fresh glands, or the injection of Evans' extract or the urine of pregnancy. In hens it stops egg laying.

The Aschheim-Zondek reaction in hydatidiform mole and malignant chorionepithelioma. Mack, H. C. and A. E. Catherwood, Am. J. Abst. & Gyn. **20**: 670. 1930.

Studies of cases of hydatidiform mole and malignant chorionepithelioma by means of the Aschheim-Zondek reaction showed that the amount of anterior-pituitary hormone excreted in the urine of these patients is greater than that excreted during normal pregnancy. The authors found that a positive pregnancy reaction could be obtained by injections of urine diluted 1 to 5 in cases of hydatidiform mole and from dilutions as high as 1 to 10 in cases of chorionepithelioma. This excessive hormone production is considered the most probable cause of lutein cysts of the ovary observed in cases of hydatidiform mole and malignant chorionepithelioma. The authors found the Aschheim-Zondek reaction to be an important diagnostic and prognostic aid in these conditions; a negative pregnancy reaction which persists after expulsion of the mole or after hysterectomy for chorionepithelioma signifying a cure, whereas a positive reaction might signify continued proliferation of mole tissue, malignant degeneration or the development of metastases. The application of the Aschheim-Zondek reaction in these conditions is illustrated by case reports.

—H. C. Mack.

The three hormone tests for early pregnancy. Mazer, C. and J. Hoffman, J. A. M. A. **96**: 19. 1931. Abst. A. M. A.

A clinical evaluation of various tests as represented by the authors is as follows: The ovarian hormones; the sex-maturation hormone of the anterior pituitary gland; Aschheim-Zondek test; the female sex hormone test, and the Siddall test. The authors conclude that the hormone tests for pregnancy are of distinct clinical value in the differential diagnosis between early pregnancy, normal or ectopic, and pathologic conditions associated with amenorrhea or irregular uterine bleeding. The female sex hormone test is the more reliable when positive in that the proportion of error in non-pregnant women is less than 4%. A rigid interpretation of the vaginal spreads and the elimination of abrupt and delayed reactions reduce this element of error considerably. The inability of the genital tract to utilize the small quantity of female sex hormone present in the circulating blood in women with ovarian deficiency results in its elimination by the kidneys; hence the occasional false positive reaction by the female sex hormone test in these cases. The compensatory pituitary hyperfunction accompanying ovarian deficiency is responsible for the comparatively large number of false positive reactions in the Aschheim-Zondek and Siddall tests. The tests performed individually render a positive reaction in about 75% of early pregnancies; when combined, the percentage of positive reactions is increased to 90, by virtue of one of the three tests showing a positive reaction. A negative finding does not exclude the possibility of pregnancy; repeated negative reactions are fairly reliable.

The midbrain pituitary problem. Michejew, W. W. and E. M. Pawljutschenko, Arch. f. Psychiat. **89**: 271. 1930. Abst., Arch. Neurol. & Psychiat. **25**: 189.

The authors discuss the relationship between the midbrain and pituitary gland with reference to the role played by them in diabetes insipidus. Five cases are reported: in three, diabetes insipidus was a prominent symptom, and in two, acromegaly. Case 1 was that of a man, aged 21, sexually underdeveloped, who had had diabetes insipidus for two and a half years before admission. This condition was more marked in the beginning than it was later. There was paralysis of the eye movement upward, with general rigidity and somnolence. The autopsy showed a tumor of the midbrain extending from the optic chiasm to the substantial perforata posterior. The pituitary body showed some atrophy. Case 2 was that of a man, aged 54, with diabetes insipidus. Here, too, the condition was more pronounced at the onset. There was a gradual development of general weakness, involvement of the lung and tumor of the liver. An autopsy revealed cancer of the bronchi and metastases in the internal organs and pituitary gland. The latter had affected the infundibulum and had spread upward into the midbrain. Case 3 was that of a man, aged 21, with diabetes insipidus following encephalitis. The diabetes insipidus had gradually diminished under pituitary treatment. Case 4 was that of a woman, aged 52, with acromegaly for twenty-two years. There was some frequency of micturition but no increase in the quantity of urine. Case 5 was that of a man, aged 55, with a pituitary tumor and signs of acromegaly, but with no definite signs of diabetes insipidus. In the five cases the author finds no

proof of any direct relationship between pituitary disease and diabetes insipidus. He comes to the following conclusions: (1) Anatomic and experimental investigations show the presence of a close connection between the midbrain and the pituitary gland. (2) A complete destruction of the pituitary gland without disturbances of the midbrain does not cause diabetes insipidus. (3) In addition to diabetes insipidus, diseases of the midbrain may also call forth signs of dystrophia adiposogenitalis.

Thymophysin temesváry. Nelson, E. E., J. A. M. A. **96:** 352. 1931. Abst., A. M. A.

In the experimental work done by Nelson, the "Thymophysin" used was obtained on the open market in May, 1930. The pituitary extract used was a lot of the same serial number of a commercial preparation of the same stated strength as "Thymophysin." This particular preparation has been examined many times and found to be uniform and to conform to the U. S. P. X requirements. He made an assay of the oxytocic and the pressor activity of thymophysin and compared the oxytocic activity of pituitary extract and thymophysin. Modification of pituitary activity by thymus was also investigated. It is his belief that there is as yet no evidence from the present investigation or in the published experiments of others to justify the conclusion that the pressor or oxytocic activities of pituitary are in any way modified by the addition of thymus extract. The theoretical considerations leading to the clinical use of a mixture of these two substances are held therefore not to be established. The clinical results obtained can be explained completely as due to the use of small doses of pituitary extract. Experimentally, no difference could be found in the pressor or oxytocic activity of pituitary alone as compared with pituitary plus thymus extracts. The strength of "Thymophysin" ampules examined by pressor and oxytocic methods was found to be from 25 to 33% of that claimed on the labels. When equivalent doses of pituitary extract and "Thymophysin" were compared on the excised uteri or on the blood pressure, no differences in action could be demonstrated.

The ovarian and pituitary changes associated with hydatidiform mole and chorioepithelioma. Novak, E. and A. K. Koff, Am. J. Obst. & Gynec. **20:** 481. 1930.

This paper is based upon the study of two cases of hydatidiform mole and two of chorioepithelioma, in all of which the ovaries were available for study, while in one of the cases of chorioephithelioma a histologic study of the pituitary was also possible. The remarkable "hyperreactio luteinalis" which probably occurs at some stage in every case of hydatidiform mole and chorioepithelioma, but which does not always assume the form of the so-called multiple lutein cysts, is definitely comparable to the ovarian changes which are produced by anterior pituitary implantations or injections. Histologic studies, such as those included in this report, and also the biochemical studies which have been described by a number of authors, leave little doubt that the anterior pituitary is the immediate cause of the lutein hyper-reaction seen in the ovaries of such cases. Our own studies indicate that the hyperluteinization involves both the granulosa and the theca interna. The histologic study of the anterior pituitary in one of our cases of chorioepithelioma showed an abnormally marked and persisting pregnancy reaction. This observation, for the first time, offers a histologic explanation for the persistence of the pregnancy test long after removal of the primary tumor, as has been reported by two or three recent authors. This abnormally persistent pregnancy reaction in the pituitary, with the persistence of the pregnancy test, is no doubt due to the presence of considerable masses of trophoblastic tissue in the metastases, as was almost certainly the case in our patient. In short, the evidence indicates that the interreaction is a triangular one, the trophoblastic increase being responsible for the pituitary reaction, and the latter, in turn, calling forth the abnormal ovarian response.—E. Novak.

An excess of serum cholesterine in animals receiving injections of urine from pregnant women (Hypercholestérinémie sérique des animaux recevant en injection l'urine de Femmes gravides). Parhon, C. I. and T. Cahane, Compt. rend. Soc. de biol. **103:** 453. 1930.

Rabbits showed such an increase which did not follow if the urine was from non-pregnant individuals.—J. C. D.

Specific-dynamic action and dystrophia adiposo-genitalis before and after treatment with pituitary preparations (Spezifisch-dynamische Wirkung und Dystrophia adiposo-genitalis vor und nach Behandlung mit Hypophysenpräparaten). Peters, J. T., Klin. Wchnschr. **9**: 1219. 1930.

The author cites Knipping's work on the specific-dynamic action in 140 normal individuals on a diet of 200 g. meat, 100 g. bread, and 50 g. butter, in connection with his own studies, and states that the physiologic variations of specific-dynamic action is between 20 and 45%. His investigations show that in obesity the fundamental change as well as the specific-dynamic action are within normal limits. However, in a special group of obesity associated with dystrophia-adiposo-genitalis the specific-dynamic action is reduced. He cites a case of dystrophia adiposo-genitalis in a girl, 19 years old, who suffered with obesity, violent headaches, spastic paresis of the lower limbs and amenorrhoea. After treatment with anterior pituitary lobe tablets, the headaches vanished, the gait improved and menstruation was established. In addition the patient's specific-dynamic action returned to normal. He considers this the first case described where the connection between specific-dynamic action, the functions of the hypophysis and the ovaries, which has been determined by animal experiments, has been clearly demonstrated in man.—H. G. Beck.

Anatomical and behavior changes produced in the rat by complete and partial extirpation of the pituitary gland. Richter, C. P. and G. B. Wislocki, Am. J. Physiol. **95**: 481. 1930.

The hypophysis was completely removed in ten adult rats and partially removed in fifteen adult animals, leaving intact either parts of the anterior lobe, or parts of both anterior and posterior lobes. The ten animals with total removal of the glands were very inactive, as was determined by means of records of running activity in revolving drums. Spontaneous activity was not affected by partial removal of the gland. Body-weight and food-intake were definitely decreased by hypophysectomy. Usually they decreased to a low level, at which they remained fairly constant. The four-day sex cycles were absent in the hypophysectomized animals, present and normal in the animals with only anterior lobe tissue remaining. In three animals, with both anterior and posterior lobe tissue present, the sex cycles were markedly disturbed. Permanent polydipsia was produced in a large fraction of the rats with the pituitary gland partially removed, but occurred in only one out of ten animals with the gland totally extirpated. Further evidence has been gained that polydipsia does not depend on the removal of the pituitary gland. The variable and often transient increase in water-intake following complete or partial hypophysectomy is presumably due to the injury of the adjacent brain-stem. The magnitude of the increase is often the same as that characteristic of the increase produced by puncture of the neighboring tuber cinereum, but the increase is transient. Injections of alkaline extract of the pituitary gland following hypophysectomy produce a definite increase in body-weight and food-intake, but have no effect on spontaneous activity or water-intake. In completely hypophysectomized rats autopsy reveals marked changes in other organs and tissues. The thyroids and adrenals are hypoplastic. The reproductive organs are atrophic. The thymus and the lymph-glands of the entire body are markedly enlarged. There is a pronounced disappearance of body fat. These changes can be obtained in a mild degree, in some instances, after incomplete removal of the pituitary.—Authors' Summary.

Concerning the hormone of the anterior lobe of the hypophysis. Follicle producing hormone (Prolan A) and tumors [Ueber Hormone des Hypophysenvorderlappens Follikelreifungshormon (Prolan A) und Tumoren]. Zondek, B., Klin Wchnschr. **9**: 1207. 1930.

A deficiency of the generative glands is conditioned by an over-production of Prolan A. The detection of it in the urine explains the cessation of the sexual functions. Prolan A occurs at times in benign and extra-genital malignant tumors, but almost regularly in genital carcinomas.—J. Gagnon.

Studies on diabetes insipidus. Bourquin, H., Am. J. Physiol. **96**: 66. 1931.

The results of injury to the hypothalamus and hypophysis of dogs allowed to survive 40 to 150 days after operation are reported. Symptoms of adiposity and dystrophy did not develop in any of these experiments, confirming Smith's

work on rats. In all of the experiments, in which diabetes insipidus developed, the lesion involved the caudal portion of the hypothalamus. There was no correlation between the site of lesion and the occurrence, intensity, or duration of the diabetes insipidus, however. Diabetes insipidus failed to develop after separation of the infundibulum from the brain stem and destruction of the tuber cinereum in 2 experiments, and after destruction of the hypophysis and entire hypothalamus with the exception of the caudal tips of the mammillary bodies in one experiment. These experiments indicate that diabetes insipidus is not a deficiency phenomenon and that the nature of the disturbance produced determines its development. Diabetes insipidus did not develop after complete destruction of hypophysis and hypothalamus in 26 acute experiments on dogs and 26 acute experiments on rabbits. It followed destruction of the hypophysis and tuber cinereum accompanied by injury to the mammillary bodies in 12 of 14 acute experiments on dogs and 12 of 18 acute experiments on rabbits. These results indicate (a) that diabetes insipidus is not a deficiency phenomenon; (b) that the mammillary bodies or centers in their vicinity are essential to the phenomenon, and (c) that the polyuria is caused by a diuretic substance or irritation to hypothetical centers controlling salt and water metabolism. Diabetes insipidus was produced by injury to the hypothalamus in 23 pigeons after transection of the brain stem caudad to the oculomotor nerves in such a way as to leave the blood supply intact but did not develop after simple transection of the brain stem at the same level. These experiments demonstrate that in pigeons descending nerve tracts are not essential to the phenomenon of diabetes insipidus confirming similar experimental evidence in dogs.—Author's Summary.

Basal metabolism and specific dynamic action of proteins in diabetes mellitus and the effect of insulin. Elmer, A. W., L. Ptaszek and M. Scheps, Ztschr. f. d. ges. exper. Med. **71**: 722. 1930. Abst., Chem. Absts. **24**: 5836.

The basal metabolic rate was within normal limits and did not parallel the severity of symptoms. The specific dynamic action of protein was normal and in no case greater than +40%. Insulin produced no definite effect on the metabolic rate but tendered toward raising the rate, while it tended to lower higher specific dynamic action and raise the lower specific dynamic action.

Hereditary diabetes mellitus. Kennedy, S., J. A. M. A. **96**: 241, 1931. Abst., A. M. A.

The author has had the opportunity to study a family in which ten cases of diabetes have occurred in two generations. The first generation consisted of twenty-eight persons, the children of Mr. A and of his two sisters, Mrs. B and Mrs. C. Five were children of Mr. A; eleven, of Mrs. B; twelve of Mrs. C. Three persons were lost trace of more than thirty-five years ago. Of the remaining twenty-five, eight developed diabetes, while seventeen did not develop diabetes; eleven are now living, fourteen have died. Of the eleven living, four have diabetes and seven are free from the disease. Of the fourteen dead, four died of diabetes, while ten died from other causes, four in infancy. In this generation there have been five amputations of a leg for diabetic gangrene; three of the patients who underwent amputation are living, two have died of diabetes. Information is lacking for only three members of this generation. In the second generation, thirty-five persons were studied. Thirteen were the grandchildren of Mrs. B, twenty-two were the grandchildren of Mrs. C. So far, only two of this generation developed diabetes. Twenty-four of the thirty-five are living, one with diabetes, twenty-three free from the disease. Eleven are dead; one died of diabetes, ten died of other causes, five in infancy. Three of this generation died of tuberculosis. Information is lacking on none of this generation, except as to such children as the three untraced persons of the first generation may have had. Of the original brother and two sisters, from whom these three branches of the family sprang, there is reason to suspect diabetes in only one, Mrs. C. Her death took place in 1896, when much less was known about this disease than now. Her age at death was 71 years. According to the account given by her family, she had leg ulcers for several years previous to her death, and for several months she had had sore toes. She had also lost a great deal of weight. Her last illness began with a cold; vomiting set in, and she went into coma and died in three or four days. At the time, her condition was diagnosed "typhoid pneumonia." The description is almost typical of acidosis but Kennedy does not include this case in his record, as it was not diagnosed diabetes by any physician at any time.

Insulin shock and the myocardium. Middleton, W. S. and W. H. Oatway, Am. J. M. Sc. **181**: 39. 1931.

Pulse, blood pressure, blood sugar and electrocardiographic studies were made on 11 patients during the height of clinical manifestations of shock and during periods of freedom from symptoms. The T wave of the electrocardiogram was reduced in amplitude during insulin shock. The more serious alterations of conduction in the heart are transient. The authors feel that there is grave danger of injury to the myocardium by insulin shock due to the limitation of glucose for energy purposes.—E. L.

Early variations of the muscle and liver glycogen in depancreatized dogs before and after injection of insulin (Les variations précoces du glycogène du foie et du muscle chez le Chien dépancréaté). Rathery, F., R. Kourilsky and S. Gilbert, Compt. rend. Soc. de biol. **103**: 378. 1930.

Fourteen dogs were used. After pancreatectomy, the liver and muscle glycogen falls. Insulin further reduces it in muscles but acts variably on the liver. There is no exact relation between blood sugar level, liver glycogen, or muscle glycogen.—J. C. D.

Hyperglycemia immediately following insulin injections in normal dogs (Hyperglycémie insulinique immédiate chez le chien normal).

The sugar content of the blood in various areas during the hyperglycemia immediately following insulin injections in normal dogs (L'hyperglycémie insulinque immédiate dans les divers territoires vasculaires chez le chien normal). Rathery, F.. R. Kourilsky and Y. Laurent, Compt. rend. Soc. de biol. **103**; 563; 565. 1930.

From studies on fourteen normal dogs, the authors conclude that insulin usually produces a transitory hyperglycemia 10-30 minutes following injection. This is independent of the variety of insulin, the dose or the mode of administration. The hyperglycemia is most marked in the hepatic veins and slightly less so in the portal vein.—J. C. D.

Clinical investigations into the effect of intravenous injection of insulin. Roholm, K., Acta med. Scandinav. **73**: 472. 1930.

The fasting secretion was examined in 9 patients with normal stomachs. The stomach content was withdrawn by continuous suction. There was found to be a definite amount of secretion, free acid, total acidity and pepsin. The gastric secretion was examined in 16 patients with normal stomachs, 9 men and 7 women, after intravenous injection of 12 international units of insulin. It was confirmed that insulin stimulates the gastric secretion quantitatively as well as qualitatively. In 13 out of 16 cases the acidity curve ran a typical course, reaching its maximum about 1 hour after the insulin injection. Mention is made of a small transitory increase of the secretion in the beginning of the experiment. By establishing normoglycemic and hyperglycemic conditions under the insulin effect, it was demonstrated that the gastric secretion has to be regarded as a hypoglycemic symptom. The threshold value of the blood sugar for the production of gastric secretion was found to be 40-50 mgm. per cent.—Author's Summary.

Modifications in anatomy and function of the pancreas in certain states of the sex life of women (Contribution á la connaissance des modifications anatomiques et fonctionelles du pancréas dans certain états de la vie génitale de la femelle). Spirito, F., Arch. di ostet. e. ginec. **16**: 1030. 1929. Abst., Rev. franc. d'endocrinol. **8**: 66.

Histological researches show a hyperfunction of the islands of Langerhans during the course of pregnancy. There is a still more marked hyperfunction after castration. Experiments to determine the insulin content of the pancreas in these two states did not furnish positive results.

Diabetes mellitus. Wendt, L. F. C. and F. B. Peck, Am. J. M. Sc. **181**: 52. 1931.

This is a review of 1073 cases of diabetes treated during the last ten years. The highest incidence was among the females from 30-70 years of age. The onset factors had the following percentages: obesity, 57.8% acute infection, 21.2%; heredity, 14.8%; physical or mental strain, 11.8%, and goiter 8.9%. There is a direct relationship between age incidence and obesity and also between arteriosclerosis and gangrene. The diabetes which develops following severe physical or mental strain is usually mild. The authors suggest that a nearly constant blood sugar may be maintained by feeding equal meals every eight hours.—E. L.

The action of atropine and adrenaline on gastric tonus and hypermotility induced by insulin hypoglycemia. Wilder, R. L. and F. W. Schultz, Am. J. Physiol. **96**: 54. 1931.

It is shown that hypermotility produced in the fasting dog's stomach by the subcutaneous injection of insulin is inhibited, and the increased tonus is lowered by giving atropine in physiologic dosage. This effect is not accompanied by any increase in the blood sugar. Adrenaline hydrochloride injected intravenously during gastric hypermotility accompanying hypoglycemia, caused a lowering of tonus and inhibition of the active stomach contractions. This effect was not due to increase in blood sugar. The experimental results would seem to suggest the possibility that the hypertonicity of the starving infant may be due to an increased central nervous irritability caused to some extent by an existing hypoglycemia.—Authors' Summary.

The action of parathyroid extract in sympathectomized animals. Bacq, Z. M. and S. Dworkin, Am. J. Physiol. **95**: 614. 1930.

Normal cats show responses (increase of blood calcium, muscular weakness, polypnea, etc.) to parathyroid extract (parathormone) essentially similar to that observed in dogs by previous investigators. Toxic symptoms occur after prolonged administration, but the time of onset does not correspond to the highest blood calcium level. In sympathectomized cats and dogs the basal level of blood calcium is not outside the average range for normal animals. The absence of central sympathetic nervous impulses does not appreciably influence the response of cats and dogs to parathyroid extract.
—Authors' Summary.

Experimental fibrous osteodystrophy (Ostitis fibrosa) in hyperparathyroid dogs. Jaffe, H. L. and A. Bodansky, J. Exper. Med. **52**: 669. 1930.

The experiments have shown that parathyroid extract (parathormone Collip) can be injected into puppies in increasing amounts for long periods without fatal results. Thus time is allowed for bone changes to develop. Long continued injection leads to progressive decalcification and resorption of the existing bone, to fibrous replacement of the marrow, and to the production of the other features characteristic of ostitis fibrosa. Deformities eventually appear. It is safe to assume that the bone changes produced by hyperparathyroidization have the same pathogenesis as those observed in clinical cases believed to be instances of hyperparathyroidism—that is. cases with a negative mineral balance and decalcification of the skeleton.—H. L. Jaffe.

Symptoms in parathyroidectomy. II. The preventive action of irradiated ergosterol in excessive doses. Comel, M., Atti d. pontif. Accad. d. Sc. Nuovi Lincei, **11**: 857. 1930. Abst., Chem. Absts. **24**: 5814.

If dogs are treated with irradiated ergosterol after parathyroidectomy, tetany and eventual death result. However, if the dogs are treated for a period of 10-24 days with very large doses (1000 times the normal dose) of irradiated ergosterol, and the parathyroids are then removed, the dogs show no symptoms of tetany; hypocalcemia appears slowly, but no hypophosphatemia. One of the dogs has lived 90 days after the parathyroidectomy, without showing any bad effects.

Bone changes in hyperparathyroidism. Compere, E. L., Surg. Gynec. Obst. **50**: 783. 1930.

A case of osteomalacia is reported in which a diagnosis of hyperparathyroidism and tumor of the parathyroid gland was made and confirmed at operation. A second parathyroid was excised and found to be normal. A resumé of 11 other cases which have points of similarity and which have been recently described is briefly discussed. Symptomatic improvement was noted in the present case following removal of the parathyroid adenoma.—Author's Abst.

Calcium and parathyroid therapy in chronic ulcerative colitis. Haskell, B. and A. Cantarow, Am. J. M. Sc. **181**: 180. 1931.

Experimental calcium studies in a group of patients with mucous colitis and in another group with ulcerative colitis, together with certain clinical features observed, suggest that in a number of cases the ulcerative lesions are secondary to a longstanding mucous colitis. The rationale of calcium and parathyroid therapy in ulcerative colitis rests upon the beneficial effect of calcium on the following existing conditions: (a) nutritional change in the tissues, with or without a disturbance of calcium partition; (b) spasticity of the colon; (c) hemorrhage. Calcium lactate or gluconate by mouth and parathyroid extract intramuscularly were administered to a group of 13 patients with ulcerative colitis. Eleven became clinically well in from four to eight weeks. Ten of these were observed over a period of from one to two and a half years. The mucosa of the lower bowel resumed a normal appearance in 8. Return of symptoms for a short period occurred in 2. The clinical and anatomic improvement, which followed rather promptly the administration of calcium and parathyroid to patients with ulcerative colitis after other forms of therapy had been unsuccessful in several of them, seems to warrant the continued use of and further observation on the effects of this form of treatment.

—Authors' Summary.

Observations of human tetany. Salvesen, H. A., Acta med. Scandinav. **74**: 13. 1930.

Of five subjects with tetany after strumectomy (all females), one died in her home a few months after the operation, the others are alive respectively 4½, 3, 4 and 4 years after the operation causing tetany. Oral administration of calcium chloride has sufficed to check all the symptoms of tetany. It is pointed out that two conditions may develop. Either a condition in which the blood calcium is kept up at a nearly normal level by calcium feeding; tetany may occur at the usual critical level of blood calcium (7 mgm. 0/0), if the calcium medication is stopped. Or a condition, in which the organism is adapted to the low blood calcium level (as low as 5 mgm. 0/0 in one patient); tetany does not occur under ordinary circumstances, but cataract may develop. These latter observations confirm the author's earlier findings in dogs. In one patient the sugar tolerance as indicated by the blood-sugar curves was lower with a low blood calcium, than with a high. In one case (No. 2) the action of ultraviolet light was shown by the rise in the blood calcium in spite of reduction in the calcium intake. There was no appreciable difference between the calcium of plasma and of serum in one case of spontaneous tetany and in two cases of chronic parathyroid insufficiency with low blood-calcium.

—Author's Summary.

Preparation of two active and specific thymic substances and their effect on the calcium and phosphate content of rabbit serum. Nitschke, A., Ztschr f. d. ges. exper. Med. **65**: 637. 1929. Abst., Chem. Absts. **24**: 5815.

From fresh calves thymus 2 extracts were prepared, one of which lowered the blood Ca and produced tetanic convulsions, the other lowered the blood phosphate also with convulsions. The Ca-lowering principle is water soluble and heat-, acid- and alkali-resistant within limits. Its potency is lost by dialysis but it does not go through the membrane. It appeared to be a relatively simple albumin-like substance. The phosphate-lowering principle was similarly stable but insoluble in water, and behaves like a fatty substance. The action of these substances is antagonistic to the parathyroid hormone.

Iodine metabolism in exophthalmic goiter and explanation of postoperative reaction following thyroidectomy (Der Jodstoffwechsel des morbus Basedowie sowie die Erklärung des postoperativen Reaktion nach Thyreoidektomie). Bier, A., Klin. Wchnschr. **9**: 819. 1930. Abst., J. A. M. A. **95**: 378.

Bier points out that until recently the postoperative reactions in patients undergoing thyroidectomy were thought to be due to an excessive amount of the thyroidal secretion that was liberated by the crushing of the thyroid during the surgical treatment. That this is not the case was proved by the fact that medication with iodine prevented or at least reduced the postoperative reaction. In order to determine the pathogenesis of the postoperative complications, the author investigated the iodine metabolism of patients with exophthalmic goiter and tested the iodine content of the blood one hour after operation. He found that the iodine content was not increased after the surgical intervention. On the contrary, the total iodine content of the blood was reduced from 5 to 10%. The author concludes that the severe postoperative reaction is not caused by an oversupply of the thyroidal secretion but rather by its acute and sudden decrease in the blood. The postoperative reaction may therefore be designated as a hypothyrocemic shock. The organism of patients with exophthalmic goiter is accustomed to a large supply of thyroidal secretion. Following surgical removal of the thyroid or of a large portion of it, the supply is cut off or considerably reduced. The tissues absorb all iodine reserves, and, if sufficient iodine is not administered, the postoperative reaction sets in.

Hypothyroidism in pregnancy. Brown, F. C., Texas State J. Med. **26**: 406. 1930.

A case of hypothyroidism is reported with the history through pregnancy and for one year following delivery, 8,880 grains of thyroid extract were given in 24 months without symptoms of overdosage. A child of the mother in the case reported was followed through its first year and showed no signs of thyroid deficiency. It is emphasized that hypothyroid states are often unrecognized because of inattention to minor complaints and signs. When diagnosed, treatment is tedious but very accurately controlled by frequent basal metabolic estimations. Pregnancy in a normal woman causes an increase in the basal metabolism, in women with hypothyroidism a marked decrease. Patients receiving thyroid therapy require an increase in medication during pregnancy and for varying periods afterwards. Cretinism is due to a deficiency in thyroid secretion in the mother and is prevented by thyroid feeding during pregnancy. Cretins have hypothyroid mothers.—R. G. H.

Secretory changes in the thyroid glands of birds (Phénomènes sécrétoires dans la glande thyroide des oiseaux). Florentin, P. and M. Weis, Compt. rend. Soc. de biol. **103**: 601. 1930.

A description of the histology of the gland. The follicles connect directly with the vascular system. In certain places there is a breaking down of secreting cells and follicles, the whole mass being discharged into the blood stream. Replacement is apparently by amitotic division.—J. C. D.

Treatment of exophthalmic goiter and of hyperthyroidism by sodium fluoride. Goldemberg, L., Prensa méd. argent. **17**: 690. 1930. Abst., J. A. M. A. **96**: 394.

In treating exophthalmic goiter and hyperthyroidism, Goldemberg has obtained good results with oral fluoride therapy. The treatment is started with 10 drops in milk four times a day of a sodium fluoride solution whose concentration varies from 1% for youths to 2.5% for adults. The dose is increased (the number of drops, not the concentration of the solution), according to the tolerance of the patient, to a maximum that ranges from 15 to 50 drops at a time, making a total of from 60 to 200 drops a day. From his experience the author reaches the following conclusions. Fluoride therapy may cause improvement or clinical recovery in patients with either a non-complicated or a grave type of exophthalmic goiter in whom either iodine therapy or roentgen therapy has failed. Non-complicated hyperthyroidism may be rapidly arrested by fluoride therapy, especially if the fluoride is administered orally, since oral fluoride therapy acts more rapidly than intravenous fluoride therapy does. In cases of exophthalmic goiter or non-complicated hyperthyroidism, the sole treatment should be sodium fluoride given orally.

If symptoms of intolerance appear, the sodium fluoride should be discontinued and ammonium fluoride should be given instead. The treatment with ammonium fluoride is given as follows: the dose for youths is 5 drops, progressing to 10 drops, of a 2% solution of ammonium fluoride, three times a day, making a total of from 15 to 30 drops daily. The dose for adults is from 10 to 20 drops of the same solution, four times a day, making a daily dose of from 40 to 80 drops. The treatment with ammonium fluoride is rather an association of the two fluorides (ammonium and sodium fluorides). Besides the oral administration of ammonium fluoride, intravenous injections of 4 to 5 cc. of a 2% solution of sodium fluoride are given. The injections are made every other day up to not more than fifteen injections for every course, followed by a rest interval of from fifteen to twenty days. Fluoride therapy by mouth may be given in a continued and prolonged form for a few months till the normalization (or at least a remarkable lowering) of the basal metabolism has been secured. Intravenous injections of sodium fluoride in the doses mentioned are harmless and may be given in some infectious diseases if the antiseptic nature of the drug is taken into consideration. The author claims priority for the method.

The acidity of the gastric contents of normal cretin and hyperthyroid rabbits. Green, M. F. and M. M. Kunde, Am. J. Physiol. **95**: 626. 1930.

The concentration of HCl of the gastric contents (normal and histamine induced) of cretin rabbits, with severe anemia and cachexia, is the same as in normal rabbits. The HCl of the gastric contents of rabbits with experimental hyperthyroidism is depressed but not absent. The total HCl of the gastric contents of normal and cretin rabbits ranges from 0.2 to 0.56%.

—Authors' Summary.

A pharmacological test in hyperthyroidism: Increased action of homatropine (Über einen pharmakologischen Test bei Hypothyreose Verstarkte Homatropinwirkung). Gut, P., Endokrinologie, **6**: 345. 1930. Abst., Physiol. Absts. **15**: 466.

In cases of hypothyroidism a drop of homatropine hydrobromide usually results in a more rapid and more durable mydriasis than in normal persons. The same may be observed in animals, and is due to diminished tone of the parasympathetic. The difference between the reaction of the hypothyroid patient and that of the normal subject is not quite sufficient to constitute an absolute test for thyroid deficiency, but may be useful in connection with metabolic tests.

The pathology and treatment of Basedow's disease and hyperthyroidism at high altitudes (Zur Pathologie und Therapie der Basedowschen Krankheit und der Hyperthyreosen im Höhenklima). Hecht, V., Wien. klin. Wchnschr. **41**: 1154; 1195. 1928.

The author is chief physician at the "Palace-Sanatorium Dr. Hecht," which is situated at approximately 3000 feet above the sea-level. The pathology of Graves' disease and hyperthyroidism as they occur in this locality is discussed and the mode of treatment adopted is outlined in detail. The average thyroid was discovered to be of diffuse hyperplastic nature, mostly soft with the isthmus quite palpable, occasionally retrosternal. The advantages of treating these patients in a special sanatorium at moderately high altitude seem obvious; such a therapeutic plan has long been advocated by clinicians. Among the cases treated were instances of post-operative recurrences, others that had undergone X-ray and radium treatment without avail, and one case of post-operative tetany. In 2 of the patients who had received X-ray treatments, the skin was badly damaged from the considerable atrophy and telangiectasis. The treatment employed at this sanatorium was, aside from climatotherapy, the application of a careful dietary characterized by a minimum of flesh proteins, hydrotherapy, electrotherapy, psychotherapy, and as improvement became obvious, graded calisthenics. Medicaments were employed symptomatically, particularly when indications referable to gastrointestinal, circulatory, and nervous systems arose. The author reports, as a result of this attention, 78.5% improved or recovered and 21.5% unimproved. These results are at least as good a showing as those obtained through surgical or roentgenological treatment.—I. B.

The size of the heart in goiter. Hurxthal, L. M., O. J. Menard and M. E. Bogan, Am. J. M. Sc. **180:** 772. 1930.

The authors recorded the heart measurements from teleoroentgenograms in a series of 200 goiter patients, 100 being in the toxic group and 100 being in the non-toxic group. The age distribution in both these groups was similar. The incidence of cardiac enlargement was 46% in the toxic cases and 41% in the non-toxic group. There was no definite relationship between the duration of the disease or weight loss and the size of the heart. The greater percentage of the enlarged hearts falls in the toxic adenomatous group which is explained on the greater incidence of cardiovascular disease. The authors feel that if hyperthyroidism causes cardiac enlargement, the degree is slight.—E. L.

Effects of diathermy of the thyroid on the basal metabolism (Influence de la diathermie de la glande thyroïde sur le metabolisme basal). Jankowski, J. and L. Ptaszek, Compt. rend. Soc. de biol. **103:** 425. 1930.

Diathermy produces a temporary fall in basal metabolism followed by a return to the former level. When such a fall has been initiated, further treatment is ineffective until the usual metabolic level has been re-established. Repeated treatments become less and less effective.—J. C. D.

The temporary control of post-operative tetany in thyroparathyroidectomized dogs by the administration of thyroid hormone. Kunde, M. M., R. M. Oslund and R. Kern, Am. J. Physiol. **96:** 45. 1931.

In approximately 55% of a series of 31 dogs, tetany following thyroparathyroidectomy was temporarily controlled by experimental hyperthyroidism. The remaining 45% died as in uncontrolled tetany. Experimental hyperthyroidism maintained the serum calcium above the tetany level for 1 to 3 weeks in 55% of a series of 31 thyro-parathyroidectomized dogs. In all thyroparathyroidectomized dogs of this series, a further decrease in the serum calcium followed the discontinuance of thyroid ingestion. In the unoperated animals, moderately severe hyperthyroidism, experimentally induced, causes an elevation in the level of the acid soluble phosphorus of the blood serum which may reach 100% above normal, with no change in the serum calcium. After thyro-parathyroidectomy, the increased concentration of the blood phosphorus persists, or shows a tendency to a still higher elevation with increased severity of the hyperthyroidism, regardless of the decrease in the serum calcium.
—Authors' Summary.

Hyperthyroidism and associated pathology. Lewis, W., Am. J. M. Sc. **181:** 65. 1931.

Postmortem studies of 12 iodin treated subjects showed that the anatomic changes in the heart and blood vessels are mainly due to coronary sclerosis, arteriosclerosis, or old rheumatic fever. Arteriosclerosis, coronary sclerosis and myocardial fibrosis when present are comparable with the age and with each other. Certain deaths, clinically resembling crisis or postoperative storm, can be ascribed, on pathologic examination, partly or largely to such causes as coronary sclerosis, myocardial failure, and early bronchopneumonia. There are no significant anatomic changes in the spleen, liver, kidneys, pancreas, adrenals, and ovaries. Compared with the pre-iodin period there are apparently fewer medical deaths, fewer cases of thyroid crisis and postoperative storm, and a lower incidence of thymicolymphatic hyperplasia. Hyperthyroidism per se has no toxic influence or direct pathologic action on the heart, but indirectly it accelerates the development and progress of pathologic lesions from other sources by causing increased work for the heart, tachycardia, and fibrillation.—Author's Summary.

Remarks on the pathogenesis of Graves' disease. Marine, D., Am. J. M. Sc. **180:** 767. 1930.

The changes in the thyroid tissue are constant but not specific. The hyperplasia is no different than in other clinical associations. The lymphoblastic tissues are hyperplastic and frequently there is a cirrhotic type of atrophic change in the liver. In the rabbit and cat a transient complex similar to Graves' disease can be induced by sublethal injury to the suprarenals. The

heat production in newborn infants increases at the time of the involution of the suprarenal cortex. In fifty cases, the feeding of a glycerol emulsion of ox suprarenal glands has caused a gain in body and body strength in Graves' disease.—E. L.

A plethysmographic study of the thyroid gland of the dog. Mason, J. B., J. Markowitz and F. C. Mann, Am. J. Physiol. **94**: 125. 1930.

A method of plethysmography of the thyroid gland has been described. The effects of various drugs on the volume of the thyroid gland have been epinephrine, nicotine, nitroglycerine, pilocarpine, acetyl choline, atropine, pituiepinephrine, nicotine, nitroglycerine, pilocarpine, acetyl choline, atropine, pituitrin, rattlesnake venom, thyroid extract and thyroxine. The following drugs had little, if any, effect: strophanthin, potassium iodide and caffein sodium benzoate. The effects on volume of the thyroid gland are recorded following stimulation of the vagus and sympathetic nerves in the neck and thorax. These experiments have demonstrated that the vasoconstrictor fibers pass to the thyroid gland by way of the sympathetic nerves. Following stimulation of the homolateral vagus nerve in the thorax, before its juncture with the sympathetic trunk, or following stimulation of the opposite vagosympathetic trunk, there is produced an increase in the volume of the thyroid gland. This was considered to be secondary to increased flow of blood consequent on the concomitant rise in blood pressure. In the researches recorded, the opportunity often presented itself for studying the reactions of hypertrophied glands to the stimuli that have been mentioned. The results were identical with what occurred in non-goitrous animals. As might be expected, changes in volume were correspondingly greater in large goitrous glands. In several instances experiments were repeated on animals that had been rendered hyperthyroid by injecting thyroxine, or by feeding desiccated thyroid gland. The results were identical, whether one substance or the other was used.

—Authors' Summary.

Level of iodine metabolism, in sanitary conditions of life, and goiter. McCarrison, R. and C. Newcomb, Indian J. M. Research, **17**: 1061. 1930. Abst., Physiol. Absts. **15**: 388.

Young rats were fed on a diet of oatmeal, patent flour, linseed meal, calcium phosphate, and sodium chloride. The diet was low in iodine and markedly deficient in vitamin A. This diet gave a level of iodine metabolism of 0.033 mgm. of iodine per litre of urine, the concentration of iodine in urine being taken as an index of iodine metabolism. This level of iodine metabolism was not associated with thyroid enlargement within 60 to 64 days when the rats were kept meticulously clean, but was associated with thyroid enlargement if they were kept under unhygienic conditions of life. The type of thyroid enlargement was a simple hypertrophy of the gland. When the level of iodine metabolism was raised to 0.085 mgm. per litre of urine by giving iodized water, this latter condition was also prevented. A statistical examination of the experimental data by C. Newcomb leads to the same conclusions.

Thyroidectomy for thyrotoxicosis in older people. Mora, J. M. and E. I. Greene, Am. J. M. Sc. **181**: 74. 1931.

A consecutive series of 200 cases of thyrotoxicosis is reported, for which thyroidectomy had been performed on patients varying in age from fifty to seventy-six years. These formed 18.8% of a consecutive series of 1060 patients. The proportion of females to males was 2.5 to 1. Sixty-six and a half per cent of the cases were primary hyperplastic thyroids, the remainder were nodular goiters. The average duration of goiter was 11.68 years; the average duration of symptoms was 23.2 months; the average interval between the appearance of the goiter and that of symptoms was 14.5 years. The outstanding symptoms in this series were weight loss, tachycardia, nervousness, tremor, weakness, palpitation and exophthalmos, in the order given. There were 30 cases of pre-operative auricular fibrillation, 27 of which were restored to normal rhythm. The average pre-operative basal metabolic rate was 41.6% above normal; the average postoperative rate was +1.1%. All of the cases, whether of the hyperplastic or adenomatous type, showed a definite response to iodin therapy pre-operatively. Of 175 patients upon whom accurate postoperative data are available, 171 were completely relieved of their thyrotoxicosis, as

measured by a fall to normal of the basal metabolic rate. There were 6 operative deaths in this series of 200 cases. The total mortality (7 deaths) of the entire series of 1060 cases, which formed the basis of this report, was 0.66%.
—Authors' Summary.

Studies on the amount of phosphorus in the cerebrum and cerebellum of parathyroidectomized and thyroparathyroidectomized dogs (Recherches sur la teneur en phosphore du cerveau et du cervelet chez les Chiens parathyroïdectomisés ou thyroparathyroïdectomisés). Parhon, C. I. and G. Werner, Compt. rend. Soc. de biol. **103:** 455. 1930.

Dogs showed a decrease in cerebral phosphorus after both operations. That of the cerebellum is less affected and after thyroparathyroidectomy scarcely varies from the normal.—J. C. D.

The combination of thyroxin and parathormone in the treatment of postoperative tetany (Thyroxin-Parathormon, die Kombinations-therapie bei postoperativer Tetanie). Stocker, H., Wien. klin. Wchnschr. **43:** 1116. 1930

By means of a combination of parathormone and thyroxin severe cases of postoperative tetany may be relieved. Parathormone soon improves the blood calcium deficiency while thyroxin regulates the phosphorus balance. Through the assistance of thyroxin the spasms are much lessened and soon all evidences of the affection are completely gone. These observations in patients confirm the author's previous studies in animals.—I. B.

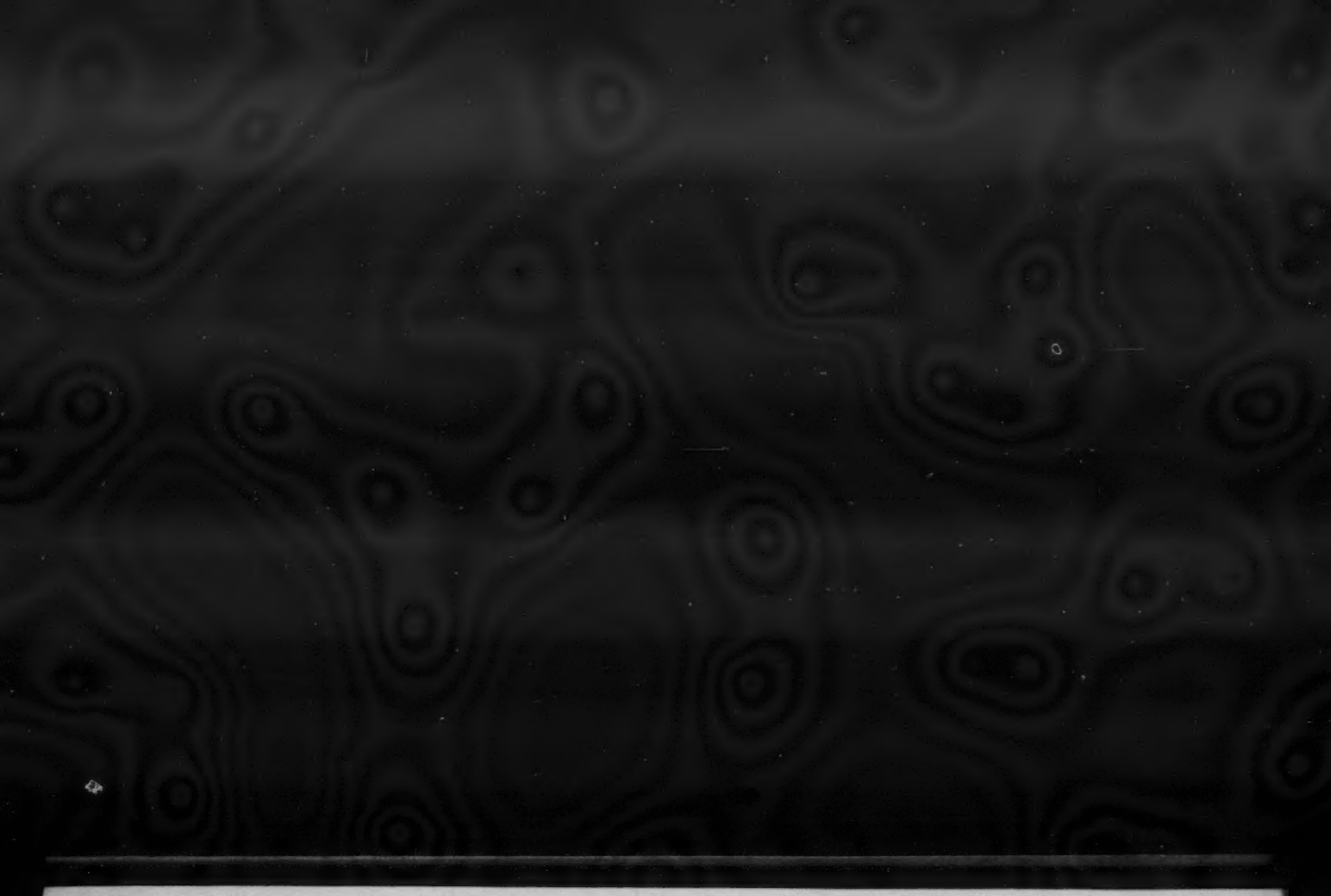
Low basal metabolism without myxedema. Thurmon, F. M. and W. O. Thompson, Arch. Int. Med. **46:** 879. 1930.

Frequent observations have been made on 196 patients with basal metabolism of 11 to 45% below the average normal (in only 8 was it lower than minus 25%), but no edema that could be detected. At least 11 patients could be considered normal (with basal metabolic rates varying from minus 11 to 24%), but it was often difficult to decide whether a patient was normal or abnormal. In 13 there appeared to be an underfunction of the thyroid which was apparently too mild to result in myxedema (so-called "hypothyroidism without myxedema"). The remaining 172 patients appeared to be suffering from various pathologic conditions but not from an underfunction of the thyroid, as judged by the clinical picture and the response to doses of desiccated thyroid sufficient to maintain the basal metabolism at a standard normal level. An extract differentiation into clinical entities is not yet possible in a large number of these cases, but a rough classification has been made, largely on the basis of symptoms. There were 79 in whom nervousness, worry and ease of fatigue were the outstanding complaints; 21 in whom scantiness or absence of menstruation was the outstanding abnormality; and 72 who suffered from various other pathologic conditions such as starvation, pituitary tumor and muscular atrophy. Muscle tone appears to be an important factor in regulating the rate of oxygen consumption under basal conditions. If the basal metabolism is lower than minus 25%, an underfunction of the thyroid is usually preseent. If the depression is less than 21% below the average normal, an underfunction of the thyroid is usually not present.—Authors' Summary.

Hypothyroidism. Warfield, L. M., J. A. M. A. **95:** 1076. 1930.

A study of 88 patients is reported. It is concluded that mild to severe grades of hypothyroidism (not myxedema) are common among persons living in a goiter region such as the Great Lakes basin. All classes of people are affected; a considerable proportion are professional men and women. Both underweight and overweight as well as normal weight are found among the patients. The most important single symptom is an undue sense of fatigue, a physical exhaustion which often leads to a neurasthenic state. Other frequent symptoms are constipation, susceptibility to mild infections such as coryza, various aches and pains, and, in women, scanty or profuse menstruation. General abdominal soreness, especially along the colon and in the right iliac fossa, is frequent. Diagnosis cannot be made without evidence of a low basal metabolic rate, as there are no pathognomonic symptoms or signs for the mild hypothyroid state. Differential diagnosis must be made from other endocrine gland failures, especially suprarenal, posterior pituitary and ovary: from such chronic diseases as (1) occult or incipient tuberculosis, (2) dia-

betes, (3) chronic nephritis, (4) pernicious anemia and other blood diseases. Rheumatic aches and pains and headaches of a migraine type may be due to thyroid failure. Thyroid extract can only normalize the nutritional needs of the body and should never be administered to reduce weight in individuals with normal thyroid function.—Author's Summary.

Abderhalden's reaction in hyperthyroidism (Zur Kritik der interferemetrischen Methode der abderhaldenschen Reaktion. II. Untersuchungen bei der basedowschen Krankheit). Zimmer, A., E. Lendel and W. Fehlow, Fermentforsch. **11**: 557. 1930. Abst., Physiol. Absts. **15**: 388.

The enzymic behavior of the blood towards thyroid, pituitary, thymus, ovary, and suprarenal substrates was studied in several cases of hyperthyroidism treated with injection of animal serum. In general the blood of hyperthyroids showed an increased activity towards thyroid, and a much diminished activity towards thymus, which returned to its normal value as the treatment progressed.